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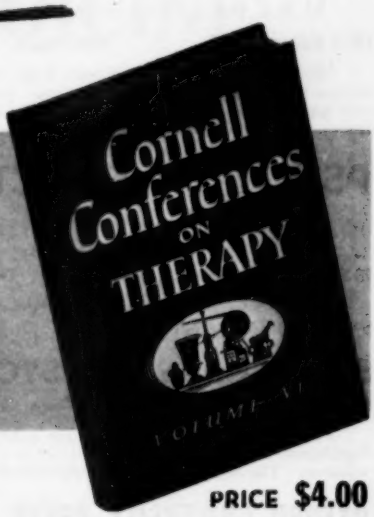

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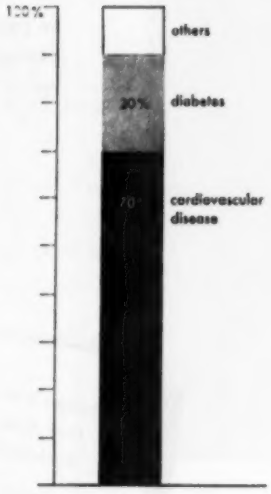

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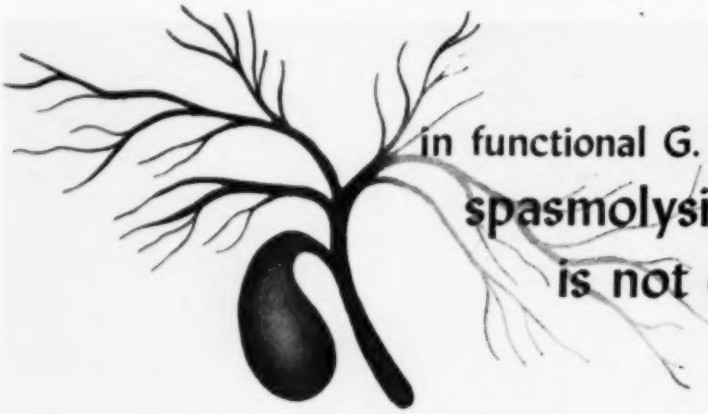

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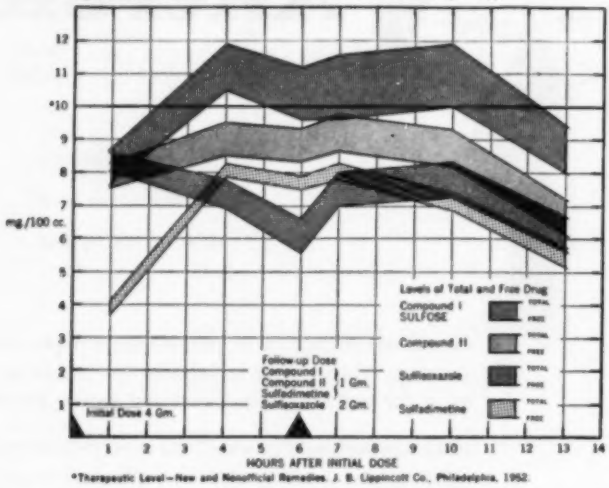

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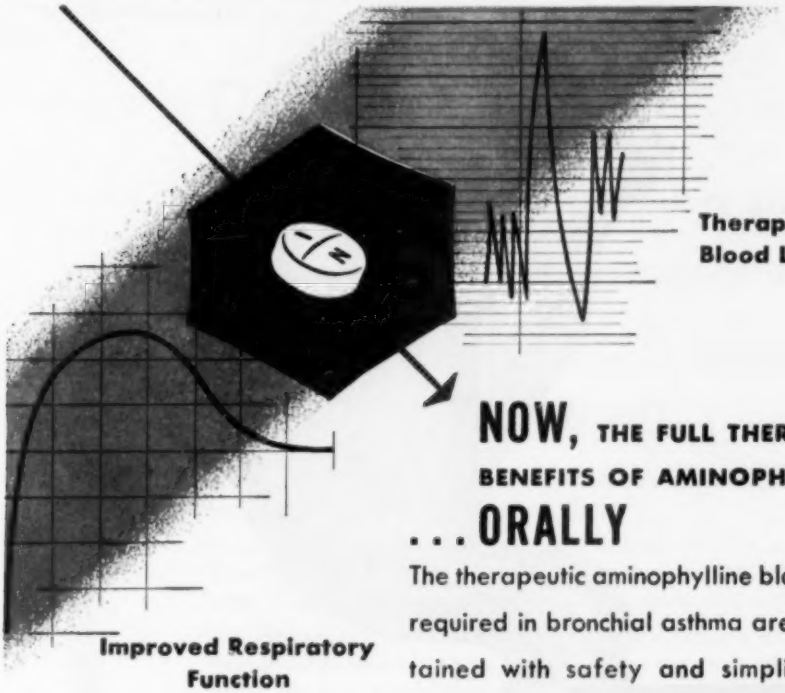

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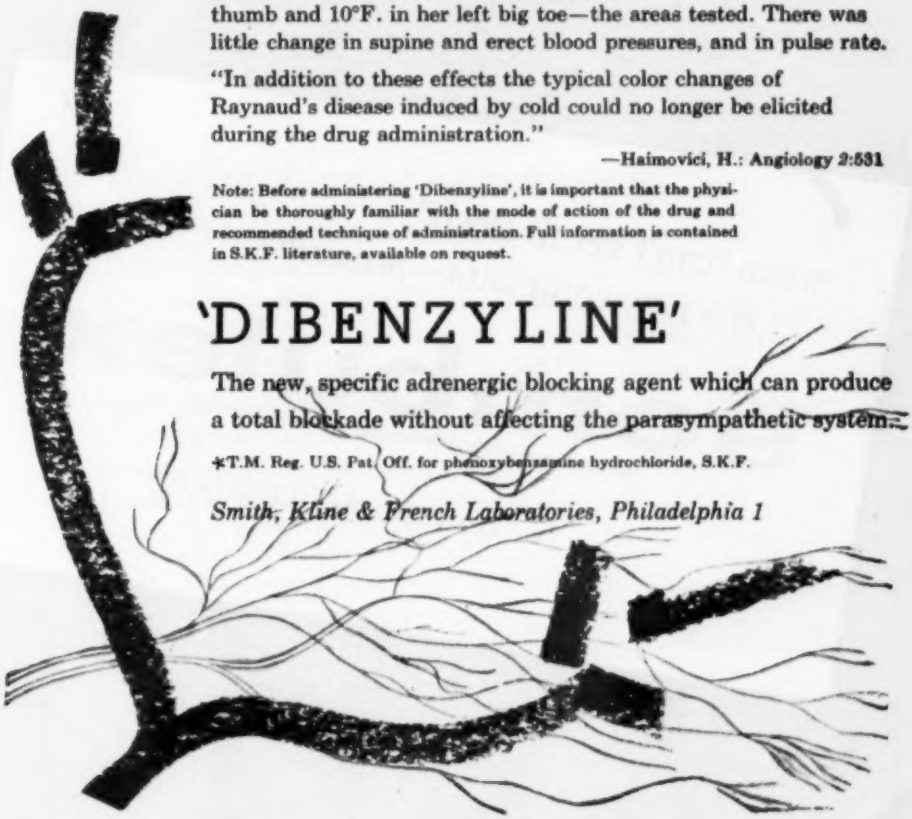

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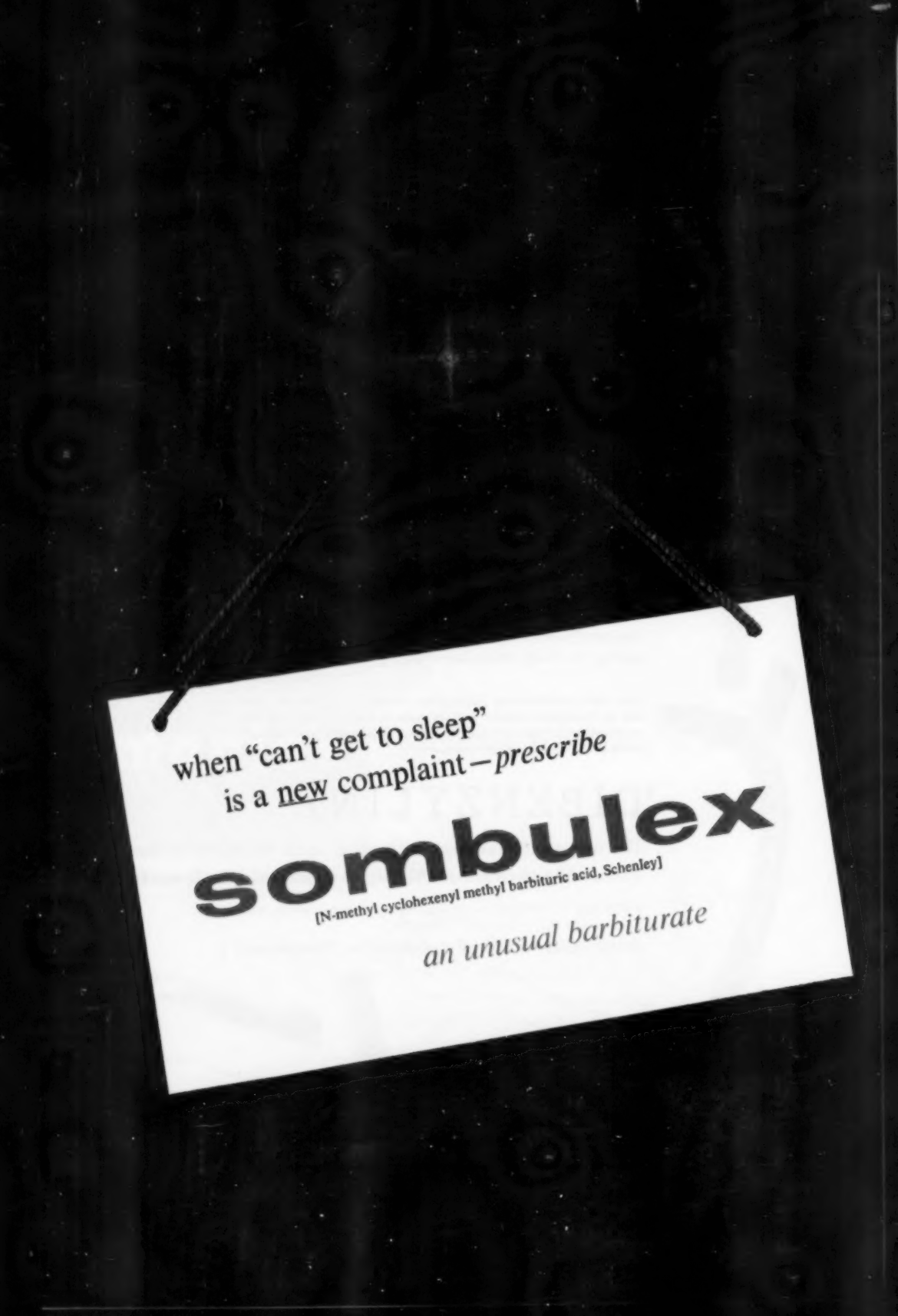
when "can't get to sleep"
is a new complaint—prescribe
sombulex
[N-methyl cyclohexenyl methyl barbituric acid, Schenley]
an unusual barbiturate

sombulex* *is an unusual barbiturate*

because it works within 15 to 30 minutes and leaves the bloodstream within 3 to 4 hours, thus avoiding the danger of hangover for patients who do not need heavy barbiturate action.

When the stresses and strains begin to tell

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Because of its rapid yet nonpersistent action, 1 SOMBULEX Tablet will help restore *interrupted* sleep without subsequent hangover, or permit a relaxing cat nap before a busy evening. One SOMBULEX Tablet also will help the new night-shift worker adjust to a daytime sleeping schedule. NOTE: The action of SOMBULEX may be too short lived for the patient already dependent upon long-acting barbiturates. SOMBULEX is supplied in bottles of 100 tablets, each containing 0.26 Gm. (4 gr.) N-methyl cyclohexenyl methyl barbituric acid, *Schenley*.

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not a simple analgesic

The striking clinical benefits of BUTAZOLIDIN in arthritis and allied disorders cannot be due solely to analgesic effect since it has only moderate analgesic effect in non-rheumatic disorders.

an effective and potent anti-arthritic

BUTAZOLIDIN produces both improvement of function and relief of pain. In rheumatoid arthritis a recent report[1] indicates "major improvement" in 40 of 68 cases. Another notes "marked decrease in swelling, increase in range of motion, and increase in strength" in 41 per cent of patients with lesser improvement in an additional nine per cent.[2] A third study[3] records "appreciable pain relief" in 69 per cent of patients with 50 per cent showing objective evidence of improvement. Similar favorable results have been recorded in gout, spondylitis, osteoarthritis, bursitis, and other painful musculoskeletal disorders. These findings illustrate that BUTAZOLIDIN when properly used provides gratifying therapeutic benefit in a wide variety of painful and disabling disorders.

(1) Kuzell, W. C., and Schaffarzick, R. W.: California Med. 77:319, 1952. (2) Stephens, C. A. L., Jr., and others: J.A.M.A. 150:1084 (Nov. 15) 1952. (3) Steinbrocker, O., and others: J.A.M.A. 150:1007 (Nov. 15) 1952.

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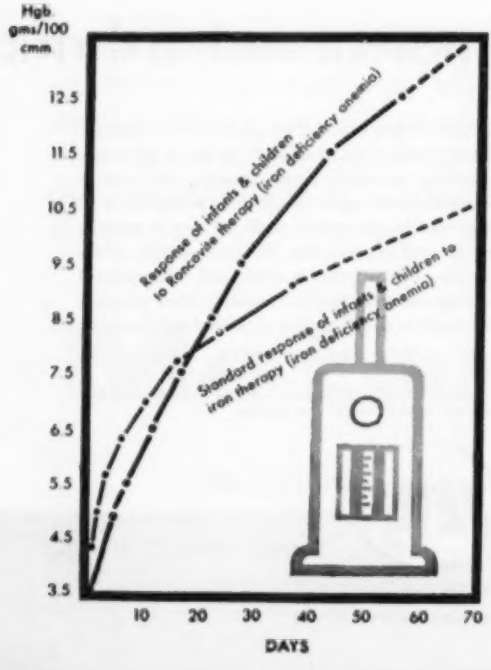
The above clinical findings mean that Roncovite offers a significant advance in the treatment of all types of "secondary" anemia.



Comparison of the response of hypochromic anemic infants and children to Roncovite and to iron; with Roncovite, iron utilization was so efficient that 58% of the ingested iron was converted to hemoglobin[2]—as compared to the usual average of 15% utilization from ferrous sulfate.—

Standard response chart, Josephs, H.: J. Pediat. 49:246 (1931).

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Tablets—each enteric coated, red tablet contains:

Cobalt chloride (Cobalt as Co...3.7 mg.).....15 mg.
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Supplied in bottles of 100 tablets.

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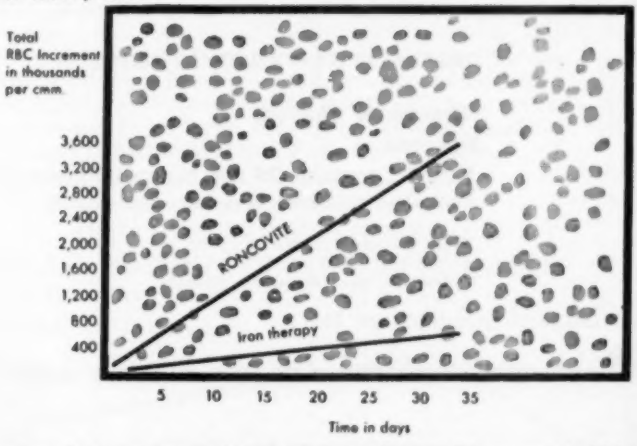
Average dose—0.6 cc. (10 minims) diluted with water, milk, fruit or vegetable juice once daily to infants and children.

Supplied in bottles of 15 cc. with calibrated dropper.

1. Wolff, H.: Med. Monatsschr. 5:239 (1951); (2) Rohe, R.J., and Bond, W.H.: to be published; (3) Berk, W., et al: New England J.M. 240:754 (May) 1949; (4) Robinson, J.C., et al: New England J.M. 240:749 (May) 1949; (5) Weissbecker, W., and Maurer, R.: Klin. Woch. 24:855 (1947; (6) Wolff, H., and Barthel, S.: Munch. M. Wschr. 93:467 (1951); (7) Gardner, F.H.: J. Lab. & Clin. M. 41:56 (Jan.) 1953.

*The pioneer cobalt product.



Comparison of the average erythrocyte response of iron-deficiency anemic children to Roncovite[2] and to iron therapy.—Computation—Method of Schiodt: Am. J. Med. Sci. 193:313 (1937).

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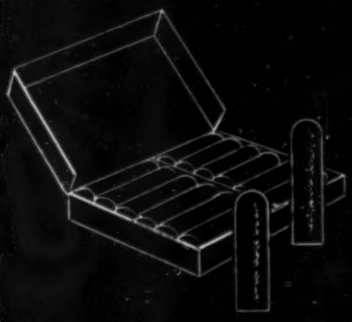

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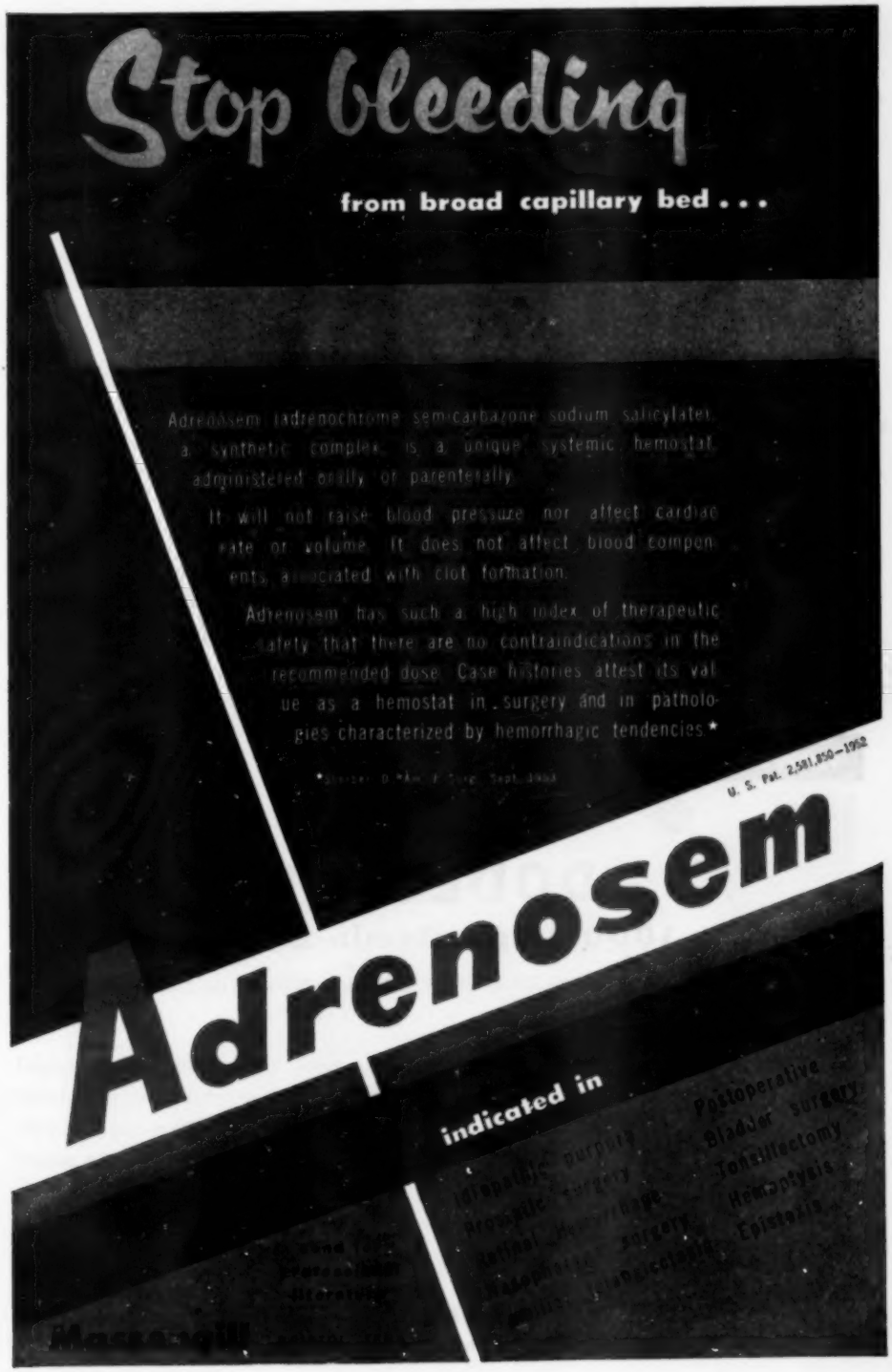
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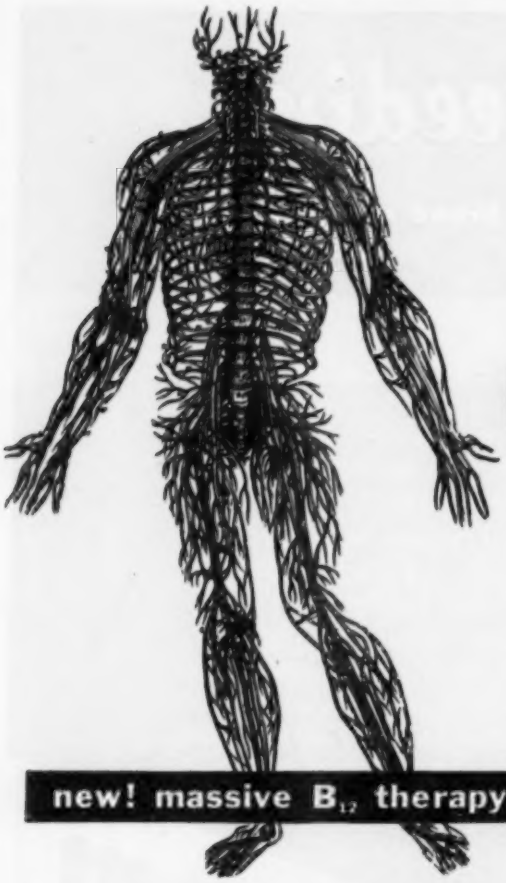

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1. Thorn, G. W., and Tyler, F. H.: *Med. Clin. North America*, 31:1081, Sept. 1947.

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(5 gr.) 0.3 Gm., (2 gr.) 0.12 Gm. with (¼ gr.) 15 mg.

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1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

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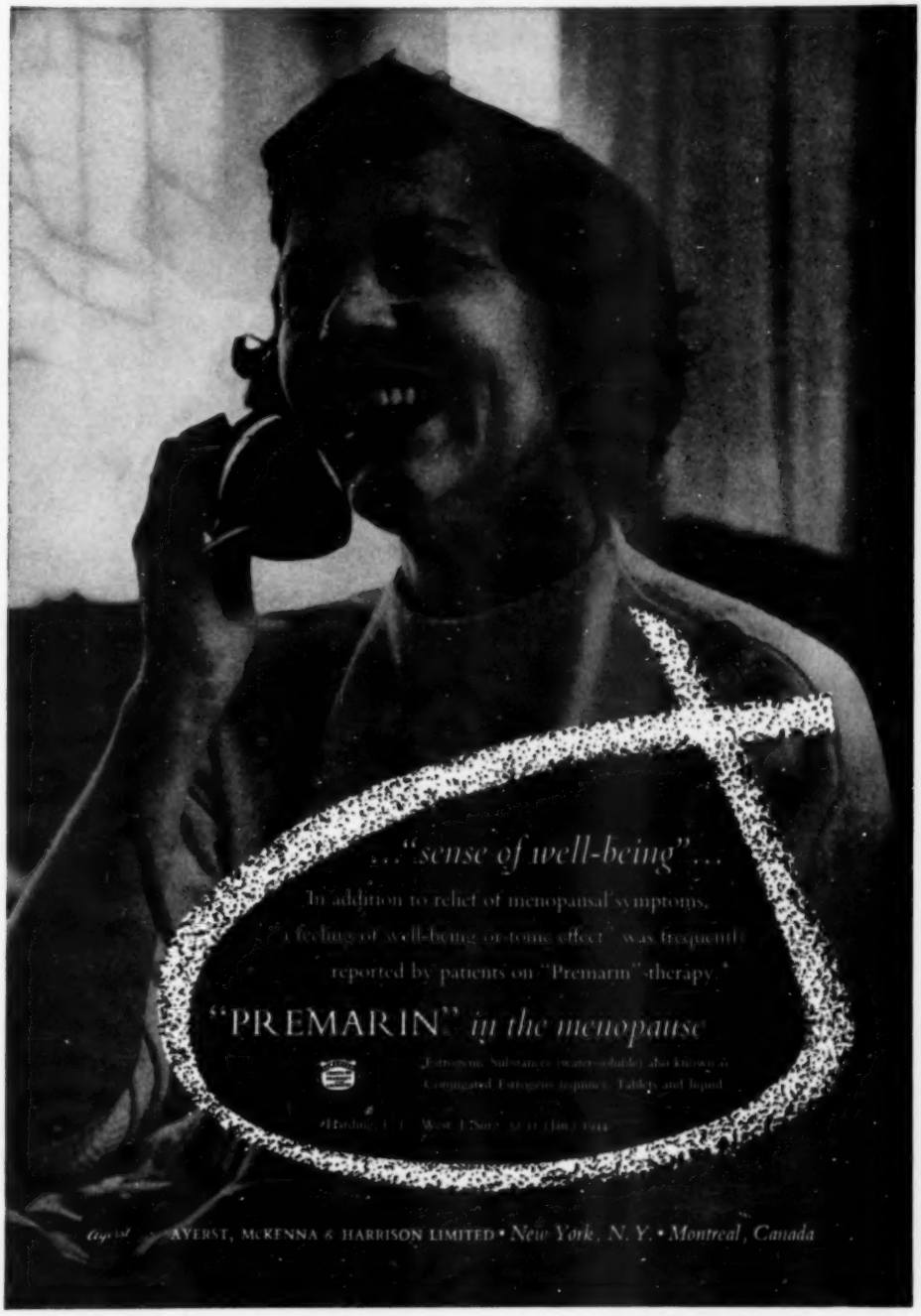
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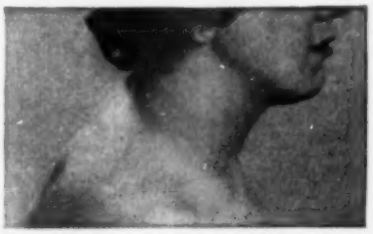
[1]Evans, R. R., and Rackemann, F. M.: *A.M.A. Arch. Int. Med.* **90**:96–127, July 1952.

Before treatment. Observe typical facies and tense sternocleidomastoid.



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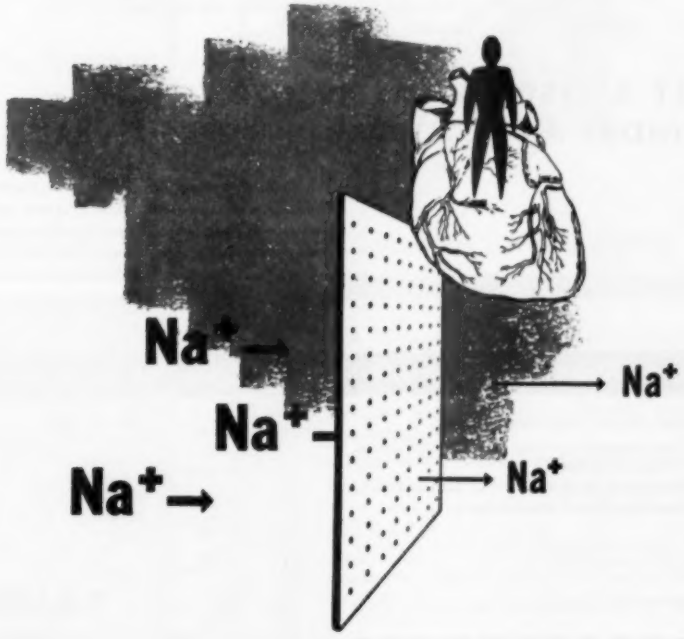

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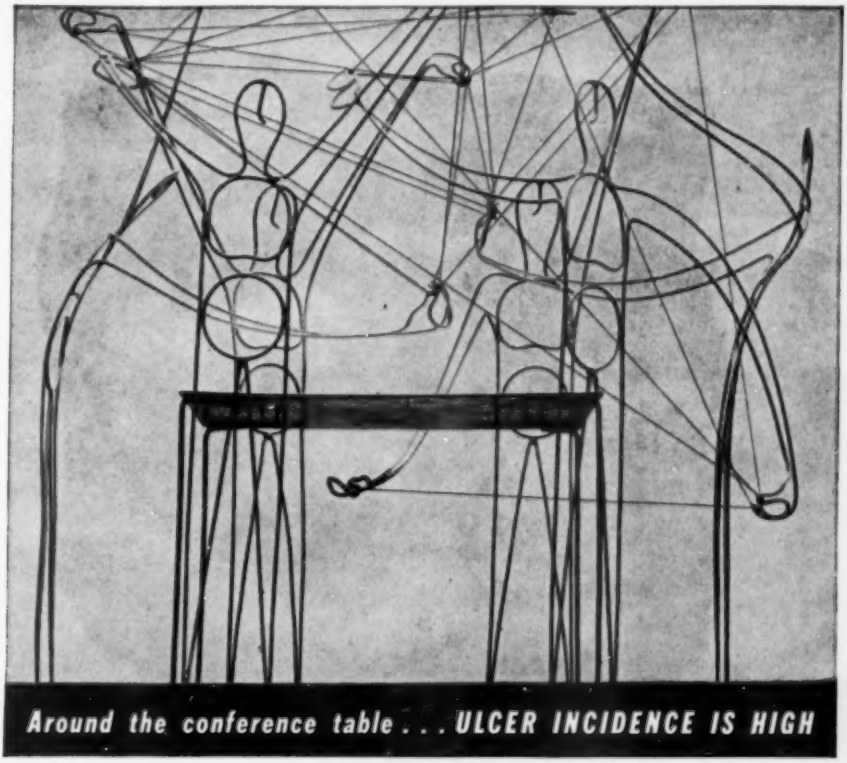

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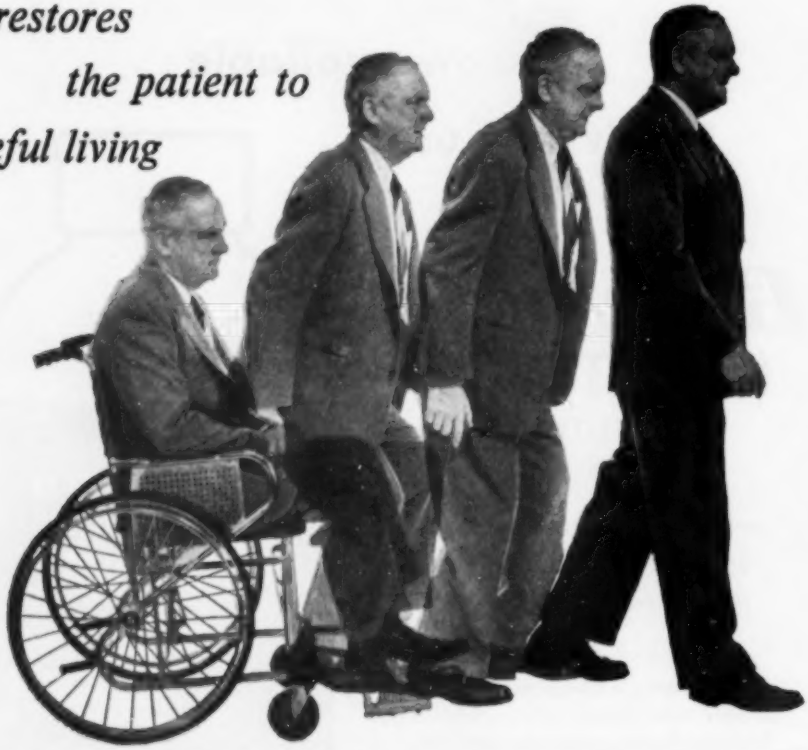

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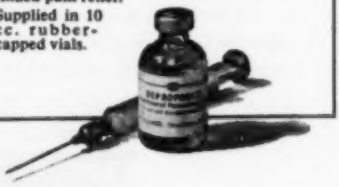

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ANNALS OF
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VOLUME 39 AUGUST, 1953 NUMBER 2

INFLUENZA: THE NEWE ACQUAYANTANCE*

By THOMAS FRANCIS, JR., M.D., *Ann Arbor, Michigan*

THE honor conferred by The American College of Physicians in naming me the James D. Bruce Memorial Lecturer in Preventive Medicine for 1953, I fully appreciate. The atmosphere in which I grew up medically, though primarily concerned with the care of the patient, constantly stimulated an interest in the broader problem of the disease itself and the biologic mechanisms involved in its occurrence. There was the hopeful attitude that not only could understanding be gained but also that it could lead to better treatment of the sick and, still further, to the ultimate objective—prevention. It was not a pattern of social philosophy but preventive medicine in the literal sense: a field for active investigation leading to the prevention of disease and disability. It has been my good fortune to have had opportunities to follow this theme even though the results are limited and the path is devious. My behavior has been merely the functioning of an organism in an environment to which it has become adapted and which it likes. It is somewhat surprising, therefore, that doing what comes naturally should elicit such a notable reward.

I did not know Dr. Bruce well, but that he could be a vigorous instrument of preventive medicine is revealed in the story of his setting up barbed wire road blocks to prevent traffic into his township when smallpox was prevalent there. His interest in postgraduate medicine was similarly vigorous. It is a pleasurable coincidence that your lecturer this year comes from the same University which Dr. Bruce served so effectively in the development of postgraduate medical education.

* Presented as the James D. Bruce Memorial Lecture on Preventive Medicine at the Thirty-Fourth Annual Session of American College of Physicians, Atlantic City, New Jersey, April 13, 1953.

From the Department of Epidemiology and Virus Laboratory, School of Public Health, University of Michigan, Ann Arbor, Michigan.

Certain of the studies referred to in this paper were conducted under the auspices of the Commission on Influenza, Armed Forces Epidemiological Board, and supported by the Office of the Surgeon General, Department of the Army, Washington, D. C.

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It is noteworthy that those distinguished men who were earlier Bruce lecturers were also exponents of the active, positive approach. Two of them —General Simmons and General Bayne-Jones, through the Army Epidemiological Board and personally—were closely associated with the studies in evaluation of influenza vaccination and furnished them effective support. I am honored to join such a stalwart company.

I have chosen to speak of influenza. It is my plan to review certain phases, particularly pandemic influenza, and to offer interpretations of its behavior in the light of our present knowledge. I would acknowledge the debt to many colleagues, ancient and recent, whose interests and contributions constitute our knowledge of influenza.

Sir Thomas Randolph, Ambassador from Queen Elizabeth I to the Court of Mary, Queen of Scots, wrote from Edinburgh in 1562 to Cecil: "Maye it please your Honor immediately upon the Queen's arrivall here, she fell acquaynted with a new disease that is common in this town, called here the Newe Acquayantance, which passed also throughe her whole Courte, neither sparing lordes, ladies nor damoysells, not so much as either Frenche or English. . . . There was no appearance of danger, nor manie that die of the disease, excepte some olde folkes. . . . I am ashamed to say that I have byne free of it, seeing it seketh acquayantance at all man's handes." [1] The statement serves to recall the fact that, over and over in its long career, an extensive prevalence of influenza has been hailed as a new disease. That it was frequently taken lightly is seen in Randolph's embarrassment at not being affected, and in various popular names—the jolly rant, the new delight, gallants' disease, the fashionable illness, and, as now, the flu or, more fashionably, this virus thing. On the other hand, the fact that the occurrences attracted considerable attention of many of the outstanding physicians during centuries in which severe disease and high mortality were commonplace indicates that there were qualities which distinguished them from other contemporary disturbances. Certain of them are repeated almost constantly in the chronicles. The sudden appearance, with the rapid, widespread involvement of all ages and kinds, is one of them. Sir Thomas Willis, outstanding epidemiologist and clinician, describes the onset in 1658: "About the end of April, suddenly a Distemper arose, as if sent by some blast of the stars, which laid hold on very many together: that in some towns, in the space of a week, above a thousand people fell sick together." [2a] He pondered that while many considered changes in temperature to be the important factor, "for the exciting the distemper, so suddenly rising, and commonly spreading, there is required, besides such an occasion, a great foregoing cause . . .; for we ought to suppose, that almost all men were prone to the receiving this disease, otherwise no evident cause could have exercised its power so potently and so many. . . ." But the epidemic period is short.

The great similarity in many of the clinical descriptions is also evident. Of the extensive epidemic of 1557 Short relates: ". . . it began with a

roughness of the jaws, small cough, then a strong fever, with a pain of the head, back and legs; some felt as though they were corded over the breast and had a weight at the stomach; all which continued to the third day at farthest; then the fever went off with a sweat, or bleeding at the nose. In some few, it turned to a pleurisy, or fatal peripneumony." [2b] With limited variations, the description is encountered over and over.

Then the feature of low mortality is prominent. The epidemic of 1580 has been called the first real pandemic, involving Asia, Europe and Africa extensively. Short states: "This disease raged all over Europe at least, and prevailed for six weeks. . . . Though all had it, few died in these countries, except such as were let blood of, or had unsound viscera." [2b]

The Thomsons speak of the occurrence of 1743 as a virulent pandemic.[3] Huxham says: "This fever seemed (in England) to have been exactly the same with that which, in the Spring was rife all over Europe, termed the 'Influenza.' . . . This fever although exceedingly common far and near, was fatal to few, since, provided that the sick kept within doors in season when they were seized with it, it generally went off on the third or fourth day." [2c] The clinical phenomena were typical. Jordan,[4a] however, states that the actual number of deaths occurring in London during the height of the epidemic was as great in proportion to the population as it was in our American cities in 1918, although it was only three times the norm.

The great prevalence of 1758 is the first with origin ascribed to America. In Scotland, Alves reports: "It was the most universal epidemic I ever saw; and am persuaded, that more people were seized with it than escaped; but it was not at all mortal here." [2d] Others agreed with this statement.

That of 1782 was called a great pandemic outbreak in Asia and Europe and has a number of interesting features. Many observers emphasized the tremendous incidence, with its peak in May in England, and although the mild three-day course was common and in many districts few died of it, there are more indications of either a mixed epidemic or more frequent complications. Some observers spoke of the illness as usually lasting seven to eight days. Herpes were repeatedly mentioned, erysipelas also, sore throat, and much more comment as to pulmonary disease. Gray believed that "it will probably appear to have differed, in some respects, from all the former disorders of the same species; and with regard to the number of persons affected by it, and the great space of the earth over which it spread its influence, to have been equalled by few of them, perhaps exceded by none." [2e] English and Italian physicians at this time strongly supported the thesis that the disease was infectious and contagious, with its own materies morbi coming from the effluvia of patients and carriers. Strikingly, in English reports of the year it was pointed out that young children and older people were less frequently affected than the middle group. Hamilton [2e] says: "I think the middle age felt it most . . . I mean from 16 to 45 or so"; Smyth [2e]: "Children and old people escaped entirely or were affected in a

slighter manner." More women were said to escape than men. The difference in age distribution is further emphasized by reports of 1790 and 1836, when the older people were again said to be most fatally affected, although adults of middle age suffered severely. A case fatality of 2.3 per cent was tabulated.[2f]

There is little to add to the description of influenza in the last century, with the exception of that in 1918. The high incidence, the low mortality, the common clinical picture, the seriousness of pneumonic complications and the similarity of accounts in different periods are consistent. On the other hand, some statements need evaluation. First, the phrase "few died of it," although quite literally meant, was not necessarily accurate, since some reporters considered deaths from pneumonia separately; in addition, it may

TABLE I

Identified Influenza Epidemics Since 1930

Swine A	A	A-prime	B	C
1930–31	(1)1932–33 late (9)1934–35			
	1936–37		1936 early	
	1938–39			
			1940 early	
	1940–41			
	1943–44			
			1945 early and prolonged	
		1947 early		+
		1950 early		+
		1951 early		
			1952 early	±
		1953 early		

have been only a relative statement, suggesting that the mortality was low in comparison with certain other diseases, such as cholera, meningitis, plague or the usual high general mortality of those periods. Second, recorders have paid less attention to the milder outbreaks. The probability that a variety of disease is mixed in the complications is apparent, but one finds that great care was taken by many of the writers to emphasize that they are not talking of the ordinary seasonal bronchial catarrh, the common cold or even the epidemic catarrh. Regardless of these reservations, first-hand experience and the historical records lead readily to basic agreement with Hirsch's statement that influenza has at all times and all places borne a stamp of uniformity in its configuration and its course.[5] His compilation of epidemics reveals that in 55 of the years from 1800 to 1875 influenza was recorded in epidemic form in various parts of the world; in eight of them it was apparently worldwide, while in a number of others much of the Eastern or Western Hemisphere was involved in a few months. But it is quite certain that many milder outbreaks were neglected by historians.

The recurrences went on in the nineteenth century, highlighted by the pandemic 1890 period and culminating in the catastrophe of 1918. Since then the well established pattern of recurrences has continued. One of the bases employed to chart epidemics of influenza and their severity, notably by Collins and his associates in the United States, is that of the excess mortality from respiratory disease which accompanies them.[6a, b] In the past 20 years identification of outbreaks by demonstration of virus has been possible, and the results of the two procedures are remarkably in agreement (figure 1). Three immunologically distinct types of influenza virus have been identified, and within the Type A, at least, significant subgroups have been recognized. During this period in the United States, combined clinical, epidemiologic

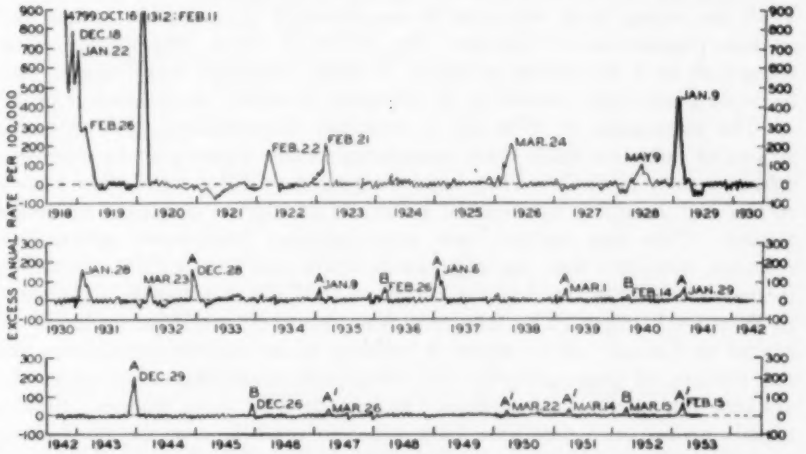

FIG. 1. Excess death rates: influenza and pneumonia. (Reproduced from Collins and Lehman, Pub. Health Reports 1951 and Morbidity and Mortality Report N.O.V.S. March 13, 1953.)

and microbiologic studies have revealed six definite epidemics of influenza A, four of influenza B, and, beginning in 1947, four of what is called A-prime (table 1). Influenza C is largely a virus in search of a disease, but serologic studies have shown it to be a widespread infection and in 1950 we identified a definite but localized epidemic.[7] In both 1936 and 1940 influenza B occurred early in the year and influenza A in the late months. But of great epidemiologic importance is the fact that, by relatively precise virus identification, the early stirrings, the spread and the distribution of an epidemic can be charted. The epidemic of 1936–37 was thus shown by independent observations of many laboratories to be worldwide. In the spring and early summer of 1943 scattered local episodes of influenza A were detected, with little significant spread until the extensive epidemic began in November of

that year, when its distribution was closely mapped. Although the activity was started on a limited scale the year before, this was the first major contribution of a continuous alert established by the Commission on Influenza, with listening posts and detection centers in laboratories throughout the United States rapidly transmitting results of diagnostic samplings. It operated in conjunction with the coördinated studies of vaccination.[8] The plan was further extended to include observations in nearly all areas where the United States Army was engaged, so that in 1945 apparently unrelated local outbreaks of influenza B were identified in widely scattered parts of the United States from March until the major epidemic build-up in November and December. During the summer it extended throughout the Pacific area, Alaska, West Indies, Canal Zone, Australia and South America. With the winter peak influenza B was detected in American troops and civilian populations in Europe. By virtue of these observations what seemed to be a discontinuous series of small outbreaks was brought into focus as a year-long prevalence of influenza B with a sharp autumn peak.[9]

The experience of 1946–48 is especially illuminating. The A-prime strains of influenza made their appearance in this country in an extensive epidemic early in 1947. They were recognized to differ from other known strains and were not significantly influenced by vaccine composed of earlier strains. This was another new acquaintance. Subsequent information revealed, however, that the same virus strain had been mildly circulating in Australia in 1946, and in the winter of 1947–48 was spottily distributed in Western Europe. The following year, however, a diffuse epidemic occurred in Europe. Here again, a building up of epidemic properties and the identity of geographically and temporally diversified occurrences developing into widespread epidemics were charted by virus studies. Strains of this group since that time have apparently taken over the dominating position in Type A epidemics, so that the worldwide influenza prevalent in 1950–51 and in the current year has been caused by A-prime viruses, whereas the characteristic A strains have not been found. In the midst of this change, however, influenza B in 1952 was recognized in pandemic distribution.

These facts demonstrate that the same virus can be responsible for apparently sporadic, limited epidemic or pandemic occurrences of influenza and that they may, in reality, represent stages in the development by the virus of epidemic properties during its adaptation to the human population. They point out, however, that although the clinical and epidemiologic characteristics of epidemic prevalences may be quite similar, the problems of waves and recurrences is a complex one, involving viruses of different immunologic character. It seems certain also that similar viruses have been responsible for the otherwise characteristic but unidentified experiences both before and after 1918. Interestingly enough, no particular bacterial agent has been a consistent, or even frequent, accompaniment of these viral outbreaks.

The fact remains that no virus was isolated from the pandemic of 1918, nor has other material been available with which to make a specific identification. Moreover, there are those who consider it to be a completely different disease, a new acquaintance. Certainly, it was an unparalleled episode in the history of influenza. Nevertheless, the clinical behavior of that 90 to 95 per cent of illnesses which were uncomplicated, the major epidemiologic pattern and the evidence of immunity in the population seem to characterize it as influenza associated with a virus which had previously been in circulation. The disagreement centers largely about the matter of age of incidence and of mortality, for which there are but limited data. The most adequate for the autumn of 1918 are those obtained by Frost and Sydenstricker by house-to-house canvass of 130,000 persons in different

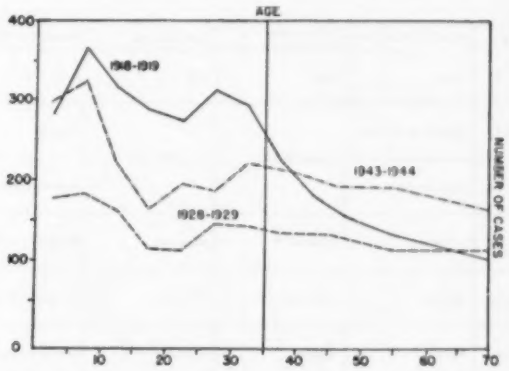

FIG. 2. Age incidence of certain respiratory diseases during two- to four-month epidemic periods in Baltimore, as recorded by special canvasses. (Redrawn from Collins, S. D.: Age and sex incidence of influenza in the epidemic of 1943–44, Pub. Health Reports **59**, fig. 1, Nov. 17, 1944.)

parts of the United States.[10] The data for subsequent epidemics are largely those reported by Collins and his associates, and except for 1928–29 are from much smaller material.[6b, 11a, b, c] When the curves of specific age incidence of total influenza, grippe, pneumonia and colds in bed, for 1918–19, 1928–29, and 1943–44 (a well-identified epidemic) are compared, there are rather great similarities up to 35 years of age.[11c] The total incidence in the three outbreaks was 246, 138 and 210 per 1,000 population, respectively (figure 2). The incidence of all cases is greatest at ages five to nine; it is lowest at 15 to 24, and rises again at 25 to 34. In 1918 this second increase was 14 per cent; in 1928, 29 per cent; in 1943, 30 per cent. These similarities suggest that there is a common pattern of immunity to the viruses involved in 1918 and other years. The curves after 35 years, however, differ in that the marked decline seen in 1918 is reflected only as a mild decrease in subsequent epidemics. One definite exception to the latter is

our own data obtained by survey during the epidemic of influenza B in 1936, when a progressive decline from a peak at five to 15 was seen.[12]

The immunologic interpretation is that children in the five to nine age group are the most susceptible to influenza (figure 3). They develop a relatively specific immunity against recent strains of virus, reflected in the low point of incidence from 15 to 24 years. The tendency to increased incidence from 25 to 40 suggests a waning effectiveness of the strain specific immunity. During this period and later, however, a broader composite immunity is being built up from repeated experiences. It is less affected by moderate strain variation and results in a reduced incidence in older ages, which holds fast in most epidemics. The absolute differences at these ages between 1918 and other epidemics are of doubtful meaning. In any case the tendency to progressive decline in incidence with age points out

Age	Incidence of Illness	% Pneumonic Complications	Case Fatality	Immunity to Virus
0-4	High	High	High	Low
5-9	Highest at all times	Lowest (5-20)	Lowest (5-20)	Lowest
10-24	Usually lowest			High-specific
25-39	Increases	Increases*	Increases	Waning of specific
40-49	Declines	Declines	Increases	Increased composite
50+	Declines*	Highest	Highest	Increased composite

*Degree varies with severity of epidemic

FIG. 3. Relation of age to features of incidence and immunity in influenza.

that the 1918 epidemic strain was not a new acquaintance immunologically, and, in fact, the similarities in incidence patterns in different epidemics strongly indicate similarities in virus composition. It is impossible from such evidence, however, to determine whether the responsible virus had been broadly in circulation shortly before the 1918 epidemic, except as the reduced incidence in the 10 to 25 year age group suggests a recently acquired resistance.

These similarities tend to emphasize the most striking dissimilarity—the excessive and disproportionate incidence of pneumonic complications in the 25 to 40 age group of 1918. It has led to the common conclusion that influenza in that year more commonly affected persons of 25 to 40, which we have seen is not the case. That they were more seriously affected than usual is adequately demonstrated by the distortion of the "normal" age curve of pneumonia [13] from its skewed U shape (lowest point, 15 to 25, and a progressive increase thereafter) to that of a W.

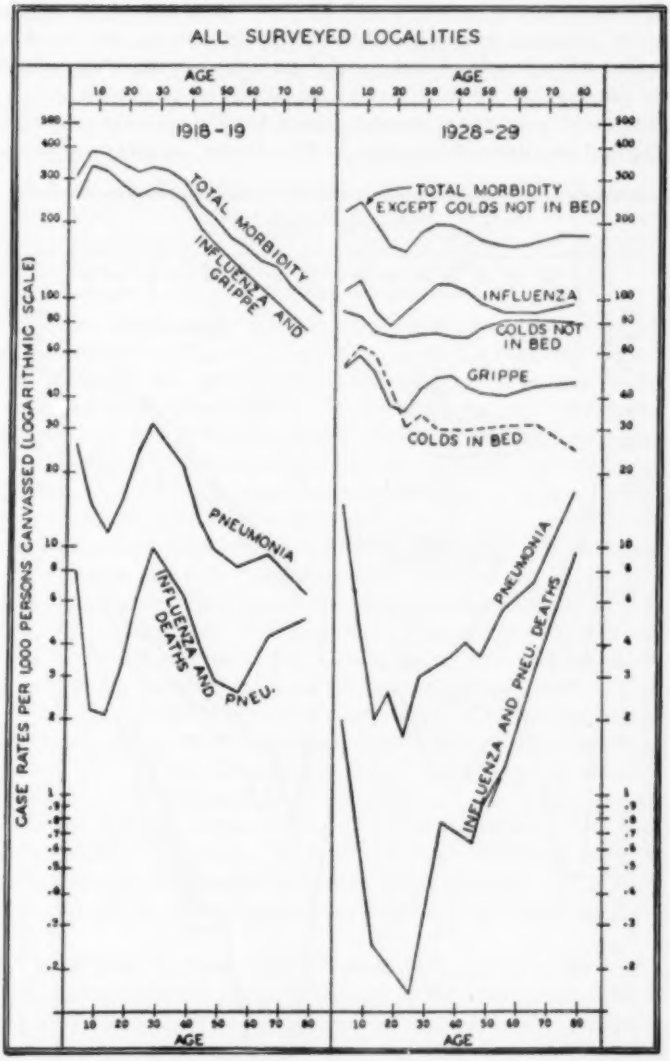

FIG. 4. Relative change with age in the incidence of the various types of respiratory illness in surveyed groups during the epidemics of 1928–29 and 1918–19. (S. C. Collins, Pub. Health Reports **46**: 1909, 1931.[118])

It is clear that the incidence of what was called pneumonia was abnormally high at all ages (figures 4 and 5).[11a, c] It is also apparent that the frequency of influenza and pneumonia was comparatively low in older persons, but that when people of that age *did* get influenza there was a high percentage of pneumonia and the highest case fatality of all groups.

The five to 14 year group presents somewhat the opposite picture. They had the highest incidence of influenza but the lowest frequency of pneumonia

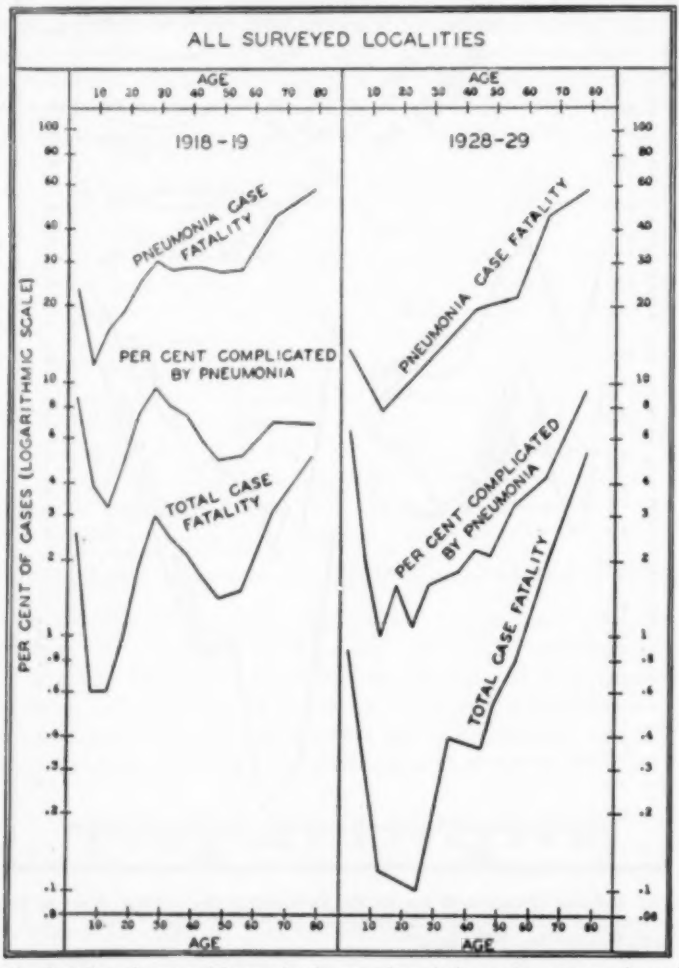

FIG. 5. Relative change with age in the severity of the various types of respiratory illness in surveyed groups during the epidemics of 1928–29 and 1918–19. (S. C. Collins, Pub. Health Reports **46**: 1909, 1931.[11a])

and fatality; they were immune to what was called pneumonia but not to influenza.

The 25 to 40 age group had an intermediate incidence of influenza, the highest frequency of pneumonic complications and a high case fatality, although less than that in the later ages.

Why did the pulmonary complications and mortality of 1918 show this abrupt change from the usual? The answers which have been offered, while meeting some aspects of the situation in a plausible manner, have generally failed to provide a satisfying explanation of the full question. In my attempt to do so, perhaps much of what I shall say will seem to be ingenious reasoning designed to avoid a simple conclusion, but nevertheless I am offering my proposals.

It becomes increasingly difficult, in view of accumulated knowledge, to accept the conclusion that war conditions were the deciding influence. Although the disease was marked in military forces, it was also severe in areas little involved in the hostilities. The dislocations and rapid mixing were much greater in World War II than in 1918. Moreover, influenza has not been historically a war disease, like typhus, jaundice and others.

There is no doubt that bacterial complications were important, but what organisms selectively attack the 20 to 40 year age group? It is not characteristic of pneumococcal infection. *Hemophilus influenzae* pneumonitis may occur at any age but it is most commonly encountered in young children. There is no evidence that hemolytic streptococcal pneumonia concentrates in adults of middle age. The significance of *Staphylococcus aureus* has probably been underestimated but, again, there is no indication that it has a predilection for persons of 25 to 40 years. I am increasingly impressed by the fact that the distinctive pathologic feature of the epidemic of 1918, extensive destruction of the respiratory epithelium and rapid metaplastic overgrowth,[14, 3, 4] is the characteristic injury produced by influenza virus. As Shope demonstrated with swine influenza,[15] the virus is the essential agent but the severity of the disease is markedly enhanced by combination with hemophilus. Similarly, ferrets carrying hemolytic streptococci or certain pasteurella after inoculation with virus exhibit a much more violent reaction, and the secondary pathologic picture is modified by the bacterial invasion.[16]

The conclusion is, then, that influenza virus was the decisive factor of 1918, producing a severe primary damage to the respiratory epithelium and creating a medium in which various bacterial agents could become implanted and produce the multiform pictures which were actually observed. This was predicated from the clinical and pathologic observations by many students of the 1918 epidemic at the time, and I am ready to believe that injury inflicted by the virus itself caused a goodly proportion of the fatal illnesses, to which bacteria were incidental.

But the data regarding the incidence of infection do *not* indicate that the

virus infection of 1918 selectively attacked the 25 to 40 group. In fact, the younger groups were more frequently affected, even though the age group five to 20 had the lowest frequency of pneumonia in 1918, in agreement with the normal age distribution of pneumonia. The proportionately low frequency of pneumonia in that group cannot, therefore, be attributed to specific viral immunity, because the attack rate of influenza was high, but it must be considered a form of protection provided by the physiologic ability of persons of that age to withstand functional injury. The same phenomenon is observed with brucellosis, typhus and other diseases.

The "normal" expectancy is that the incidence and mortality from pneumonia begin to rise at about 25 years of age and increase in almost linear fashion with advancing years.[13] My suggestion is that the increased incidence of pneumonia in the 25 to 40 age group of 1918 represents the expected increment at that age. In terms of the normal curve, it should have continued progressively to a much higher level in the succeeding years. On the contrary, it was actually interrupted and declined, paralleling the continuing decrease in attack rate of the essential viral infection brought about by an effective acquired immunity to the virus. Given the virus infection, older persons developed complications and fatal disease with the same frequency as in other years, showing again that they were subject to pneumonia when injury occurred. The result is, then, not that the 20 to 40 age group in 1918 was selectively more subject to pneumonia than older persons, but that the latter were less susceptible to influenza, thereby escaping the viral injury which determined the likelihood of developing pneumonia (see figures 4 and 5).

The combined effect is that the middle age group possessed a lower margin of the physiologic tolerance which protected the five to 24 year group from pneumonia, and a less complete resistance to the virus than that which protected the older ages against the essential virus injury (figure 6). It shows, instead, the results of a high incidence of influenza and the increased liability of its age to pneumonia and fatality following influenza virus infection.

Here it is well to recall one or two points presented earlier. I would emphasize again that at all ages the incidence and the fatality were exceptionally high in 1918, and that immunity in the first decades of life is essentially strain-specific, its breadth of effectiveness related to the antigenic structure of the strains which have been and are to be encountered. The incidence curve of 1918 indicates that the virus attacked almost a fixed percentage of susceptibles at all ages. Consequently, the declining slope indicates that the population had in years not too long prior to 1918 encountered virus bearing antigenic resemblances to the pandemic strain, but that the effect of that experience was more solidly effective beyond 35 to 40 years. The more virulent a strain, the greater, presumably, is its ability to override the lesser degrees of resistance. An epidemic caused by a mild

strain would obviously affect children most prominently. A highly infectious and highly virulent strain would, according to the immunologic thesis I have presented, exhibit its effects upon a population just as that of 1918 did, especially if the virus were not antigenically a completely new acquaintance. The curve of incidence should be pushed up and to the left; pneumonia should be observed excessively and earlier in adult life than usual, much of it viral in character. At the same time, the firm composite immunity of multiple experience would be effective in maintaining a level of resistance which would limit the incidence of virulent virus infection in the upper ages, just as it does the less severe infections of other years. Essentially, all the differences between the 1918 pandemic and prevalences of other years can be explained in terms of virulence of the virus.

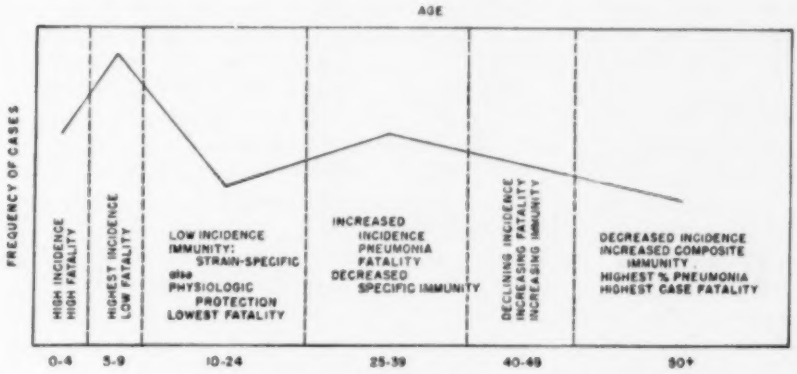

FIG. 6. Relation of age to features of incidence and immunity in influenza.

Although the degree of antigenic variation can play a rôle, it is important to emphasize that the characteristics which make for virulence are likely to be independent of antigenic constitution in the usual sense. For example, the epidemic of 1947, which introduced the A-prime strains to this country, was mild, showing little evidence of disturbing the age incidence or of seriously affecting the mortality.[11d] The 1918 data clearly demonstrate that the virus of that autumn was not an entirely new acquaintance antigenically. Even the sharper decline of the incidence in the group above 40 may be only a comparative difference from the higher incidence in younger ages; the actual difference from the levels observed at that age in other years is small and may be related to the severity of the epidemics compared and other features inherent in the data, rather than an indication of significant differences in immunity.

In consequence, it is my tendency to attribute the major unique characteristics of the autumnal pandemic of 1918 to the primary injury created by

a highly virulent virus having antigenic similarities to strains which had been in circulation earlier. A significant question remains as to the time and extent of its previous dissemination. There is little adequate basis upon which to reach a conclusion. The outbreak of 1890 nowhere had the severity of 1918. It did not produce a dislocation in age of mortality in Massachusetts resembling that of 1918, although there was a definite excess of mortality in the 20 to 40 year age group,[4b] and Jordan [4b] concluded that the age distribution of notified cases in 1890 indicated a "proportionately high attack rate among young adults." This was not the case in the pandemic of 1847. I have previously mentioned the indications of the same type of shift in 1782; there is no doubt that the incidence was high in 1782, and it is my impression that the clinical complications appear to have been more confusing than in certain other periods, thus suggesting a multiplicity of agents involved. But these similarities in pandemic periods resemble more the influence of high infectivity and increased virulence than evidence of serologic identity of the strains involved. If, however, the 1918 pandemic were caused by the same antigenic strain as that of 1890, it is curious that it should have induced a specific immunity of such duration unless this were also true of epidemics in recent years caused by closely related strains of virus. It is somewhat difficult for me to believe that the 1918 virus was simply a reappearance of an old virus of fixed high virulence and that it alone can cause pandemic influenza.

An alternative view is that it was a virus which, during its circulation in the population, developed an unusual capacity for virulence. In this respect the virus of the autumn of 1918 was a new acquaintance. Support for the concept of an adaptation is available. Mention has already been made of how, in the spring and summer of 1943, scattered outbreaks of influenza A preceded the epidemic of the following winter; and how, in 1945, influenza B circulated widely for eight months before the sharp epidemic began in the fall. In 1946–48 the actual development of epidemic potential by the new A-prime strains was charted over the globe.

There is little doubt that the strains of recent years have been much less damaging. Shope and I,[17] for example, while studying the infection of swine with the PR8 strain of human origin, noted that it failed at times to establish in the swine the *H. influenzae suis* given at the same time—in marked contrast to the swine virus. On several occasions in recent years epidemics have entered populations under investigation in whom hemolytic streptococcal infection was prevalent without inducing increased bacterial invasion.[18] At Sioux Falls, Hodges and MacLeod [19] noted that while pneumococcal pneumonia was epidemic on the post, the entrance of influenza epidemics resulted in an increased incidence of pneumonia but the ratio of upper respiratory infection to pneumonia was little affected. On the other hand, epidemics of influenza still result in an increase of pneumonia

and excess mortality in the usually vulnerable age groups—the very young and the old. The outbreak of 1943, according to Collins,[11d] presented the highest total incidence of disease since 1918, and though of low fatality, the excessive incidence resulted in an excess mortality exceeded since 1918 only by the epidemic of 1928–29 (figure 7). A variety of organisms has

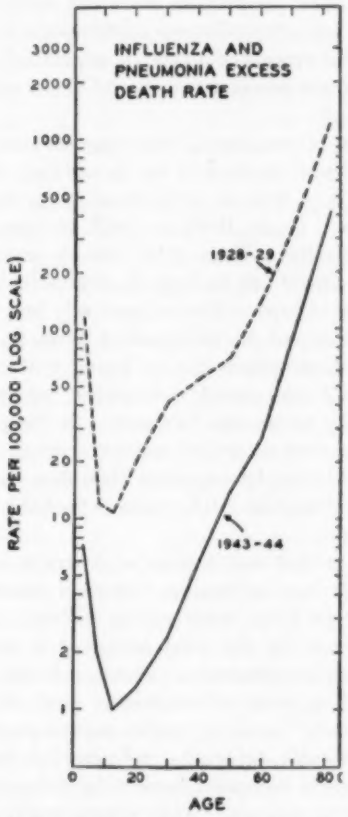

FIG. 7. (S. C. Collins, Pub. Health Reports 60: 821–853, 1945.[4b])

been found in fatal cases, notably staphylococcus, associated with extensive damage to tracheal and bronchial epithelium. Stuart-Harris [20] has pointed out, too, that these fatalities occur despite chemotherapy. The data support the conclusion that the primary determining factor in the development of fatal infection is the viral constitution and the degree of injury it creates. The effect occurs despite the fact that recent years have witnessed a decline

in incidence and mortality from pneumonia and from many other infections, a distinct alteration in the epidemic constitution.

What, then, is the outlook? To some, the fact that the viruses encountered from one year to another are changing in antigenic makeup creates a hopeless situation. I am, however, impressed with the relatively small changes which take place, suggesting that a limited number of components is being rearranged to produce different strains within a type. It may be that the mild character of many contemporary, identified epidemics is tied to the fact that the strains of a type in sequential outbreaks are closely related and the broader composite resistance of the population tends to limit their ease of adaptation.[21]

Moreover, a pattern is developing that suggests that there are periods of strain prevalence. I have mentioned the possibility that resemblances of epidemics of the 1920's to that of 1918 have suggested similarity in constitution of the viruses. From 1934 to 1943, at least, strains of Type A had a reasonable similarity. Since 1947 the A-prime strains have been dominant. Moderate alterations in Type B strains have also been observed. It is apparent that these strains differ antigenically but, in addition, the ones which spread have developed an independent property of high infectivity, so that essentially the same strain can be found within a limited period in widely separate parts of the world. A major antigenic variation would have greater opportunity to become epidemic. If the possible changes were unlimited, extensive mixing of strains showing much greater difference in antigenic constitution should be expected than has been observed. These are also reasons why I think the 1918 strain is probably related antigenically to those of recent years.

The evidence is clear that vaccination with strains of a certain antigenic constitution provides protection against influenza caused by strains of that character.[21, 22a, b] The problem with which different laboratories are engaged is that of determining the total antigenic structure in the hope of combining the necessary components to create a broad effectiveness similar to that acquired after long years of experience with infection. The studies of Salk and his associates,[23] working under the auspices of the Commission on Influenza with practicable adjuvants, indicate that the height and breadth of immunity can be greatly increased thereby by enhancing the immunogenic effect of the different components. The general application of this principle is not remote. Protection against virulent strains which arise would also be obtainable with a composite vaccine if the proper antigenic components are included, for (to repeat) virulence is to a large extent independent of antigenic structure. This is readily seen in the adaptation of influenza virus to animals; it becomes fatally virulent without major alterations in antigenic makeup, although recognizable changes like those between recent epidemic strains may be demonstrated. But animals can be protected against the virulent strain by immunization with the original strain of low

pathogenicity. It is even possible that variations can be forced sufficiently to yield the desired strains.

This is all very well, but suppose virus of the 1918 variety *is* of fixed antigenic and virulent character, recurring as the experience of the population wanes? Is there a way to estimate its composition in advance? The only significant suggestion is that the swine influenza virus is the 1918 strain, a proposal advanced originally by Laidlaw and by Shope. Antibodies to that virus are demonstrable in the serum of the human population. In 1936 Shope, and Andrewes, Laidlaw and Smith, observed that they were commonly found in persons over 10 years of age but quite infrequently below that age. It was suggested that these antibodies were the result of specific infection with the 1918 virus which in 1935 was no longer prevalent in man but had become established in swine.[17] On the other hand, swine virus is related to other strains of Type A influenza virus, and we had noted that repeated inoculations with the latter strains induced immunity and antibodies to the swine virus.[24] It seemed to us that, from this point of view, antibody to swine virus observed in man was instead the result of a broadened, composite antibody spectrum stimulated by repeated exposures to the related human strains. In support of this concept are the repeated observations that persons recovering from identified infection with later Type A viruses may exhibit a rise in antibodies to swine virus, in some instances even in young children having their earliest experience with influenza virus, Type A. In addition, we have shown that repeated vaccination with a single human A strain may also induce antibodies to swine virus in children. And as late as the 1951 epidemic, antibodies to swine virus have been shown to develop in persons under 20 years of age. No cases of influenza caused by swine virus have been detected in man during these years, although swine have been found with antibodies to later human strains. The answer is not yet complete, but recent studies in our laboratory suggest that the age at which antibodies to the swine virus are now commonly found is later than was previously the case.[25] Whatever the answer, it is clear that strains having cross-relationship with swine virus have been prominent in human epidemics. Accordingly, if that virus represents the pandemic disease of 1918, it can be incorporated in vaccine. Once again, however, I raise the question as to whether any single strain is *the "pandemic" strain*, but with proper virulence, a variety of strains can produce the effect.

I have attempted to review the characteristics of the pandemic disease of 1918 in the broad framework of our knowledge of influenza and influenza viruses. Although we are confronted with a changing population of new acquaintances, it is apparent that they represent a body of old associates varying in virulence and in antigenic characteristics. As the knowledge of their antigenic components increases, the probability that they can be countered by vaccine of proper composition improves, thus leading to the prevention and control of the last of the unconquered plagues of mankind.

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CLINICAL AND LABORATORY OBSERVATIONS ON BRUCELLA MELITENSIS IN EGYPT: STUDY OF 100 CASES *

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ALTHOUGH brucellosis has received much attention in recent medical literature, there have been few reports of the disease in Egypt and the Middle East.[1] During the period of January, 1950, to March, 1952, 100 patients were treated at this institution with various antibiotics for culturally proved caprine brucellosis.[2] The inference seems justified that the disease is relatively common in this area but that it is infrequently recognized due to the diagnostic difficulties it presents. This problem in diagnosis is by no means regional, and for this reason it seems worth while to report the clinical and laboratory features of brucellosis as observed in these patients.

CLINICAL DATA

Selection of Cases: Patients with undiagnosed fever, or patients who were apparently convalescing from such fevers, were screened from Egyptian government hospitals on the basis of the brucella agglutination test. Those patients with a persistent titer of 1:80 or above and a suggestive history were transferred to this institution and investigated further by routine laboratory procedures, including at least four blood and three urine cultures for brucella. Of 106 cases considered clinically to have brucellosis, 100 (94.3 per cent) were proved bacteriologically. Only the latter cases will be considered in the present report.

Sex Incidence: Of the 100 patients, only four were females. This unusual distribution is artificial and is due to the fact that convenient facilities for hospitalizing females were not available.

Age: No search for pediatric cases was made. The ages of patients ranged from 10 years to 70 years, averaging 34.9. Seventy-three of the patients were in the age group of 15 to 40 years.

Source of Infection: History of immediate contact with goats, with or without consumption of goat milk, was obtained in 35 cases. Ingestion of raw or improperly boiled cow or buffalo milk or of fresh cheese from these sources was possibly the source of infection in another 63 cases. Three

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of the latter cases were from families in which another member had been ill with brucellosis. Included were two cases of laboratory-acquired infection among personnel working with the cultures.

Onset and Duration of Symptoms: The onset (table 1) was acute in 62 patients, being ushered in by a chill in 47 of these. Of the remaining 15 patients with a sudden onset, four denied chills, and in 11 the history was indefinite except as to the suddenness of illness. In 38 cases the onset was insidious. These patients complained of symptoms of weakness, malaise,

TABLE I

Incidence of Symptoms and Abnormal Physical Signs in 100 Cases of Brucellosis

Onset	
Acute	62
Insidious	38
Chills	47
Fever	100
Arthralgia	64
Neuromuscular manifestations	84
Headache	80
Backache	26
Mental symptoms	7
Dermatologic manifestations	4
Gastrointestinal manifestations	40
Anorexia	23
Abdominal pain	14
Constipation	11
Nausea and vomiting	8
Diarrhea	4
Respiratory manifestations	37
Cough	20
Physical signs	31
Genitourinary manifestations	53
Albuminuria	50
Epididymitis	4
Epididymo-orchitis	2
Orchitis	2
Lymphadenopathy	73
Splenomegaly	54
Hepatomegaly	39

headache or joint aches for a period of from two to 14 days before having a high fever or being obliged to take to bed. Duration of symptoms before admission averaged seven weeks, with a range of from five days to one year. According to Spink's classification of cases by duration of illness,[8] 93 were acute (three months or less), six were subacute (three to 12 months), and one was chronic (12 months and over).

Fever: The maximal recorded temperature for each patient before treatment ranged from 100.4° F. to 106.2° F. (rectal), with an average of 103.3° F. An intermittent type of fever, with normal values in the morning and elevations in the afternoon or evening, was seen in 55 cases, these being on the whole the mildly ill. A persistently elevated temperature was observed in 31 patients, and they were generally more severely ill. Fourteen patients had minimal fever during the first few days. The latter were

therefore held for further observation and showed an undulating form of temperature curve. Clinically, the severity of illness in this group was comparable to that of the patients with intermittent fever and, in fact, when these patients became febrile they had an intermittent type of curve.

It should be noted that the period of observation before treatment started was less than one week in all of the patients except those 14 classified as undulant. The possibility exists that some of the other patients might have been classified as undulant on further observation.

Arthralgia: Painful joints were a complaint of 64 patients. The knee, shoulder, ankle, elbow, hip and wrist were affected, in that order of frequency. In an occasional patient there were some joint tenderness and slight limitation of movement, but other signs of active arthritis, such as warmth and redness of skin or effusion, were not seen. Although those patients with the most marked symptoms were examined radiographically, no changes attributable to brucellosis were detected in the joints.

Neuromuscular Manifestation: Headache, a common complaint, was noted in 80 patients. It was usually an early symptom and in some cases occurred a few days before the onset of fever. In general, its severity paralleled the elevation of temperature. Generalized muscular aches and pains also were common. Low backache occurred in 26 cases.

Mental symptoms in the form of apathy, delirium, insomnia and mental confusion were noticed in seven cases. In one of these lumbar puncture was performed. There was no abnormality in the cell count or protein level, and culture of the spinal fluid was negative.

Dermatologic Manifestations: A single lesion characteristic of erythema nodosum appeared in three patients following the institution of antibiotic therapy. In each the lesion consisted of an exquisitely tender, indurated area about 1 to 2 inches in diameter. The induration was superficial and the overlying skin dusky red and warm. In two patients this eruption occurred over the lateral surface of the tibia, and in the third it overlay the olecranon process. In the former cases the inflammatory reaction persisted for 10 days, in the latter for only four days. In all cases the lesions disappeared without abscess formation or residual pigmentation.

In one patient a maculopapular rash appeared on the fifth day of fever. The distribution was centripetal, being more marked on the chest, abdomen, back and buttocks, rare on the extremities, and absent on the face. By the end of one week the lesions had disappeared. No other skin rashes were observed, but it should be noted that the majority of patients in this series were dark-skinned.

Gastrointestinal Manifestations: These were relatively common and generally occurred in the more severe cases. The onset was accompanied by anorexia in 23 patients, by nausea and vomiting in eight, and by diarrhea in four. At some time during the illness, abdominal pain was a complaint of 14 patients.

Respiratory Manifestations: Thirty-seven of the patients had at least one symptom or sign of pulmonary involvement. Productive cough was noted by 20, 14 of whom had associated physical signs such as rhonchi, râles or dullness. Another 17 patients had positive physical signs without cough. All of the patients in this study were examined radiographically, but in only two of the above 37 was there evidence of pneumonitis. In both cases it was localized and resolved on treatment for brucellosis.

Genitourinary Manifestations: Epididymitis occurred in six patients, two of whom also had orchitis. Orchitis alone was seen in two cases. In all, these complications were transient and did not result in suppuration or atrophy. In view of the fact that these patients were catheterized frequently, a possible causal relationship with brucellosis cannot be definitely established. It is to be noted, however, that no instances of infectious prostatitis, urethritis or cystitis occurred following catheterization.

Lymphadenopathy: This was noted in 73 patients. The lymph nodes commonly affected were the anterior and posterior cervical, axillary and sometimes the epitrochlear groups. Generally the nodes were small, firm, discrete and nontender.

Hepatomegaly and Splenomegaly: Physical examination revealed enlargement of the liver in 64 patients and of the spleen in 83. Owing to the high incidence of bilharzial hepatosplenomegaly, it was difficult to distinguish between enlargement due to brucellosis and that due to a previous or concomitant infestation with bilharzia. However, the presence of tenderness or enlargement which decreased or disappeared on treatment was considered presumptive evidence that the findings were a manifestation of brucellosis. Judged by these criteria, 39 patients showed hepatic enlargement due to brucellosis and 54 showed splenic enlargement.

Laboratory Data

Serum Agglutination Test: Results from this test performed on the 100 patients at admission are shown in figure 1. Repeat agglutination tests were done during hospitalization and following discharge. The average agglutination titer (figure 2) dropped slightly during antibiotic therapy and continued to decrease during the following four to eight months. In 11 of 45 patients (24 per cent) seen at eight months, the titer was less than 1:80.

Cultures: If the patient was febrile, four blood cultures and at least three urine cultures were taken during the first week following admission. If the patient was afebrile, more cultures were taken. The culture technic used was that described by Castaneda,[4] modified by the use of a tryptose agar medium. For urine cultures, crystal violet, in a final dilution of 1:700,000, was added to the culture medium to inhibit contaminants. Typing of the organisms isolated was done on the basis of bacteriostatic action of dyes and by the use of absorbed typing sera.

A total of 831 pretreatment cultures for brucella was performed on the patients in this series. Of 452 blood cultures, 317 (70 per cent) were positive, and of 379 urine cultures, 69 (18 per cent) were positive. On 370 occasions, simultaneous blood and urine cultures were obtained. Among such paired cultures, the organism was recovered from at least one of these sources in 305 (76 per cent). The distribution of the positive cultures was such, however, that brucella was cultured from the blood of all the

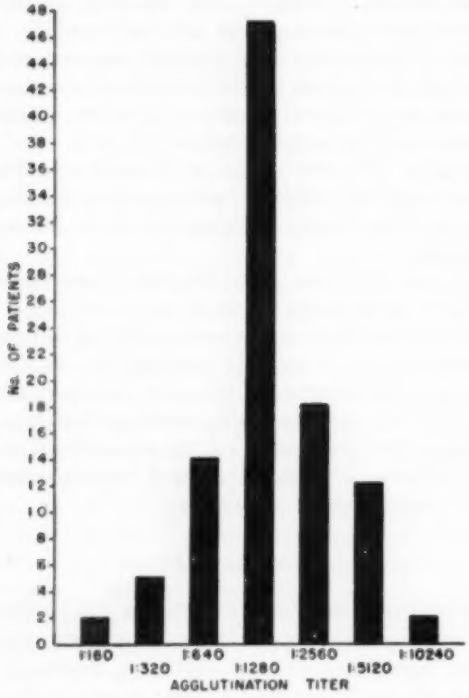

FIG. 1. Admission brucella agglutinations in 100 patients with brucellosis due to *Brucella melitensis*.

patients and from the urine of 41 on at least one occasion. In no patient was the organism recovered only from the urine. In 13 patients, positive blood cultures were obtained during afebrile periods. In two patients the organism was not recovered until a sixth pair of cultures was obtained.

Hematologic Findings: In 45 patients, the leukocyte count was less than 5,000; in 51, it was within normal limits, and in four there was a slight leukocytosis. Lymphocytosis, usually relative but sometimes with an actual increase in lymphocytes, was found in 69 cases.

Anemia of the hypochromic type was a feature in 73 cases. Other etiologic factors, such as hookworm infestation, nutritional deficiency and bilharziasis, were common among the patients and probably produced anemia in many.

The erythrocyte sedimentation rate was consistently elevated. The average initial value in 97 patients was 26 mm. in 60 minutes (Cutler). However, as the erythrocyte sedimentation rate did not on the whole drop materially after the disease was treated, the elevation was probably not entirely dependent on brucella infection.

Urinalysis: A transitory febrile albuminuria without cells or casts occurred in 50 patients.

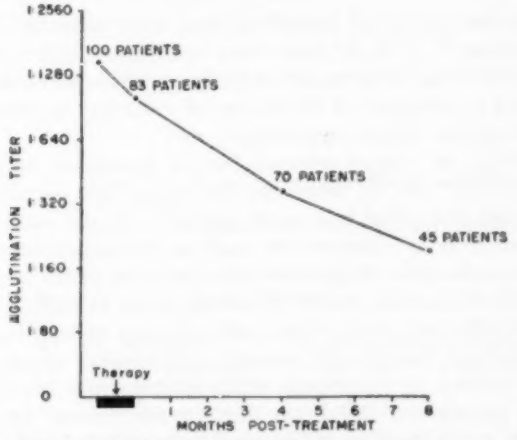

FIG. 2. Averaged agglutination titers, showing a gradual decrease during and following antibiotic treatment.

COMMENTS

Although infection with *Brucella abortus* has been shown to occur in cattle and buffaloes in Egypt,[5] no case of human brucellosis due to this species was found in the present series of 100 cases. The explanation is not clear, but may be due in part to the fact that human contact with goats and sheep is much more frequent than with other animals. Another explanation may be related to the higher invasiveness of *Br. melitensis* for man. For this reason Evans[6] states: "The proportion of human infections with the melitensis variety to infections with the abortus variety will be far greater than the proportion between the two varieties occurring in cattle." A third factor, which cannot be evaluated in this study, is related to the generally milder nature of abortus infections. People in this area whose illnesses are mild frequently do not seek medical aid, and therefore would not have been available for investigation.

The ease with which brucella infection is acquired by laboratory personnel has been widely recognized. In a review of laboratory-acquired infections,[7] brucellosis headed the list of bacterial infection. Two such cases occurred during study of the present series. During centrifugation a tube of living brucella organisms was broken, and it is believed that both workers were infected while cleaning the centrifuge after this accident.

It is usually only in cases of laboratory accidents that the incubation period can be determined with any degree of accuracy. In the present two cases, the onset of the symptoms was 11 days after the accident in one case and four months in the other. However, the possibility that infection was acquired on some occasion prior to or following that date cannot be ruled out.

The incubation period of brucellosis had been estimated by others as ranging from three to 15 days,[8] from three to 21 days [9] and from a few days to two months.[10] This wide variation in the duration of incubation is generally attributed to variation in the degree of virulence of strains, the mode of inoculation and the dose of inoculum.

The possibility of contact transmission of brucellosis between humans has been considered [10] but its occurrence has never been proved.[15] Multiple acute cases in one household have been reported, but the source of infection has been shown to be a common one, such as contaminated milk or water supply. There were three instances in this series in which two members of the same household became acutely ill within seven to eight days. A common source of infection, such as raw milk or fresh cheese, seems probable, but the possibility of human (to human) transmission cannot be excluded.

Of all the patients in the present study with positive brucella agglutinations, a high proportion (94.3 per cent) were proved bacteriologically. This is in part attributable to the cultural technics used and in part to the repeated efforts at isolation from each patient. Castaneda [11] obtained positive blood cultures from 83 of 100 patients with positive agglutination titers, but he does not state how many cultures were taken on each patient. On a single blood culture, only 70 per cent of the 100 patients in this report would have been positive, demonstrating the need for repeated efforts to isolate the organism in suspected cases.

As in this study, other authors have observed falls in agglutination titers after apparent recovery.[11, 12] However, it should be noted that some patients still had "diagnostic" titers eight months after apparently successful treatment. In these cases the agglutinations are not indicative of continuing infection, for they occur on a falling scale.

Experience with this series of patients has shown that the diagnosis of brucellosis should be entertained in every case of fever of over one week's duration, especially if accompanied by generalized myalgia and arthralgia without more obvious localization to some particular organ system. The presence of these symptoms, even in the absence of fever, should be suggestive.

If there have been previous episodes of a similar nature, or a history of exposure to infection, the suspicion should be strengthened. Generalized lymphadenopathy, a palpable, tender spleen and a leukopenic or normal blood picture are suggestive findings. The probability is enhanced if brucella agglutinins are discovered in the blood in a titer of 1:80 or above. The diagnosis can be established, however, only by isolation of the causative organism.

Summary

1. Among 106 patients selected on the basis of agglutination titers for brucella, 100 had positive blood cultures and 41 had positive urine cultures. *Br. melitensis* was the only species isolated.

2. Clinical, laboratory and epidemiologic data of these 100 cases are presented.

3. Three instances of two simultaneous cases of brucellosis in the same family are reported.

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PERICARDIAL EFFUSION ASSOCIATED WITH MYXEDEMA*

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Introduction

"Myxedema heart" was first described as a clinical entity by Zondek [1] in 1918. His description of the abnormal findings in patients with myxedema included enlargement of the heart, feeble cardiac pulsations, slow heart rate, normal blood pressure and reduced voltage in the electrocardiogram. These changes were found to be completely reversible upon treatment with thyroid hormone. Since this initial report there have been numerous observations [2-8] confirming Zondek's findings.

The nature of the pathologic changes accounting for these cardiac disturbances has been a matter of some disagreement in the literature. The suggested changes include cardiac dilatation, fibrosis of the myocardium, interstitial edema of the myocardium and pericardial effusion. The data provided by the available autopsy studies are insufficient to clarify this problem.[9-12] There is clinical evidence, however, which strongly suggests that pericardial effusion occurs frequently and is an important factor in accounting for the findings in so-called "myxedema heart." This evidence will be reviewed and two cases of "myxedema heart" with proved pericardial effusions will be described.

Case Reports

Case 1. The first patient was a 33 year old Negro housewife (table 1) admitted to Presbyterian Hospital on April 4, 1951, complaining of recurrent episodes of dyspnea, abdominal swelling and bilateral ankle edema of five years' duration. Her past history and family history were noncontributory.

Five years prior to admission the patient first noted the gradual onset of progressive ease of fatigue, dyspnea on walking one-half block, and orthopnea relieved by two pillows. A roentgenogram of the chest taken at that time was reported to have shown cardiac enlargement. Digitalization gave no apparent relief of symptoms. A pericardial paracentesis productive of 1,200 c.c. of straw-colored fluid resulted in definite and prompt relief of dyspnea and orthopnea. Following this the patient had repeated episodes of dyspnea and orthopnea which were associated with abdominal swelling and ankle edema and required pericardial paracentesis for relief on nine occasions during the four years prior to her admission to Presbyterian Hospital.

The amount of fluid removed by these pericardial paracenteses ranged between 150 and 1,800 c.c. In 1948 a study of the pericardial fluid showed a specific gravity of 1.016, protein content of 7.1 gm. per cent, and a cell count of 360 fresh red blood cells per cubic millimeter. Cultures of the fluid were negative. In addition, the

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patient was found to have 3,400,000 red blood cells per cubic millimeter; hemoglobin, 13 gm. per cent; erythrocyte sedimentation rate (Westergren), 41 mm. in one hour; total serum protein of 8.5 gm. per cent, with albumin of 3.5 gm. per cent and globulin, 4.9 gm. per cent by the Howe method.

Three years prior to admission the patient was given a six weeks course of streptomycin therapy (dosage unknown), on the presumption that she might have tuberculous pericarditis. This therapy was without benefit, though the patient developed depression of the labyrinthine function.

For two years prior to admission the patient had noted some mental slowness and memory defect. Dryness of the skin had been present for three or four years. There was no change in her voice other than hoarseness associated with dyspnea. There was no history of thermal preference. There was no change in nails or hair, and no deafness. Menses were normal. The patient gave no history of goiter or thyroidectomy, or of radiation to the thyroid area.

Physical examination on admission revealed a female appearing to be her stated age. She was dyspneic while lying flat in bed, and the respirations were 26 per

TABLE I

Case 1, Myxedema with Pericardial Effusion

Date	Wt., lbs.	TD/IDC,** cm.	EKG	BMR, %	Ser. Chol., mg.%	Thyroid Therapy, mg.
4-5-51	148	23.5/24.5	Low voltage isoelectric T-waves			
4-20-51	137			−48	271	
4-24-51	133		No change	−45		12
4-28-51	132					30
5-15-51	139*	22.0/24.5				60
5-31-51	131*			−34		90
6-22-51	126*	21.4/24.5		−20		180
7-24-51	120*	13.2/24.5	Normal	− 7	122	150

* With clothing.
** TD/IDC = Total diameter of heart/internal diameter of chest.

minute. She was afebrile. Speech was normal. Mucous membranes were pallid. Her skin was dry and scaly and of moderate turgor. Hair was fine and firm. Vision, fundi, hearing (audiograms) and tongue were normal. There was no venous distention. The thyroid gland was not palpable. Dullness was present at the bases of both lungs posteriorly, with decreased breath sounds at the right base and bronchovesicular breath sounds and medium moist râles from the inferior angle of the scapula to the base on the left. Blood pressure was 100/85 mm. of Hg in both arms. Heart rate was 78 and regular. The apical impulse was not palpable. Cardiac dullness was percussed over the entire left anterior chest from the third to the sixth left intercostal space, and 7 cm. to the right in the fourth intercostal space. Heart sounds were distant. A_2 equaled P_2. There were no murmurs. The liver edge could be palpated 1 cm. below the right costal margin, and it was slightly tender and firm. There was no ascites. Moderate bilateral pitting pretibial edema was present. Neurologic examination was normal except for sluggish relaxation of the ankle jerks.

Laboratory data revealed a normochromic normocytic anemia, with a hemoglobin of 9.5 gm. per cent; red blood cells, 2,930,000 per cubic millimeter; a normal white blood cell count and differential; erythrocyte sedimentation rate, 68 mm. in one hour. Total serum proteins were 7.8 gm. per cent; albumin, 4.3 gm. per cent; globulin, 3.5 gm. per cent; serum sodium, 144 mEq./L.; potassium, 4.1 mEq./L.; calcium, 10.0 mg.

per cent; phosphorus, 2.5 mg. per cent. Alkaline phosphatase was 1.9 Bodansky units. There was no retention of bromsulfalein after 30 minutes. Cephalin flocculation was negative. Blood urea nitrogen was 8 mg. per cent. Urine concentrated to 1.020 on a urine concentration test. Sixty per cent of phenolsulfonphthalein was excreted after two hours. Urine showed albumin 1 plus, with no glucose and negative microscopic examination. The Mazzini test was negative, and tuberculin skin test with Old Tuberculin 1 : 1000 was positive.

A roentgenogram of the chest showed an enlarged heart with pericardial contour extending almost all the way across the chest from the left lateral chest to about 1 cm. medial to the right chest wall. There was fluid in the chest and lung fissure but no evidence of pulmonary congestion. On fluoroscopy pulsations could be seen but they were very slight. Angiocardiograms revealed no evidence of abnormality of any of the cardiac chambers. Electrocardiogram showed ventricular rate of 80, P-R interval of 0.17 second, low voltage with T_1, T_2, T-V_1, T-V_2, T-V_6 isoelectric. Circulation time (arm-to-tongue) with Decholin was 28 seconds. Blood volume by the

TABLE II

Case 2, Myxedema with Pericardial Effusion

Date	Wt., lbs.	TD/IDC,* cm.	EEG	BMR, %	Ser. Chol., mg.%	Thyroid Therapy, mg.
12-4-51	143	22.0/25.8	Low voltage inverted T_2, T_3, TaVF			
12-12-51	136			−21	290	
12-24-51	135	23.5/25.8		−20		15
12-31-51	134	18.0/25.8	Increased voltage	−11		15
1-14-52	130			− 6		30
2-5-52	134	18.0/25.8		−23	331	60
3-21-52	131			−15	283	None for 3 weeks
5-2-52	130					Thyroxin 0/3
6-13-52	125	14.8/25.5		− 3		60
9-22-52	130					60
10-6-52	130	15.3/25.6				

* TD/IDC = Total diameter of heart/internal diameter of chest.

T-1824 method was 3,330 c.c. Basal metabolic rate was minus 48 per cent; radioactive iodine uptake was 7 per cent over the thyroid gland after 24 hours. Serum cholesterol was 271 mg. per cent.

On the day following the patient's admission to the hospital a pericardial paracentesis was performed and 840 c.c. of straw colored fluid were removed. The fluid had a specific gravity of 1.030, total protein of 6.1 gm. per cent, 8 white blood cells and 4 red blood cells per cubic millimeter. Aerobic and anaerobic cultures, as well as cultures on Dubos' media and guinea pig inoculation for tuberculosis, were negative.

Following this pericardial paracentesis there was prompt relief of the patient's symptoms of dyspnea and orthopnea. Venous pressure in the antecubital vein, which was 140 mm. saline prior to the tap, was reduced to 60 mm. of saline. There was no appreciable decrease in size of the heart by roentgenogram. During the 36 hours following the paracentesis the patient lost six pounds. She had a total weight loss of 15 pounds during the initial 20 days of hospitalization. In addition to pericardial paracentesis, therapy included a strict low salt diet, mercurial diuretics and hospital rest (but not bed-rest). On the twentieth day of hospitalization the administration of thyroid extract was begun 12 mg. daily, and when the patient was discharged from the hospital four days later she was taking 30 mg. daily.

During the initial three months of thyroid therapy there was a gradual improvement in the patient's exercise tolerance and a decrease in sluggishness and ease of fatigue, associated with a further weight loss of 13 pounds. There was a decrease in the transverse diameter of the heart of 10 cm., with disappearance of the pleural effusion, return of the electrocardiogram to normal, and an increase in the basal metabolic rate and a decrease in the serum cholesterol to within normal limits. Her anemia persisted, with hemoglobin of 9.5 gm. per cent, and the erythrocyte sedimentation rate remained elevated at 60 mm. per hour. During this three month period, dosage of thyroid extract was gradually increased to 180 mg. daily. At present, 17 months following the institution of thyroid therapy, the patient is entirely asymp-

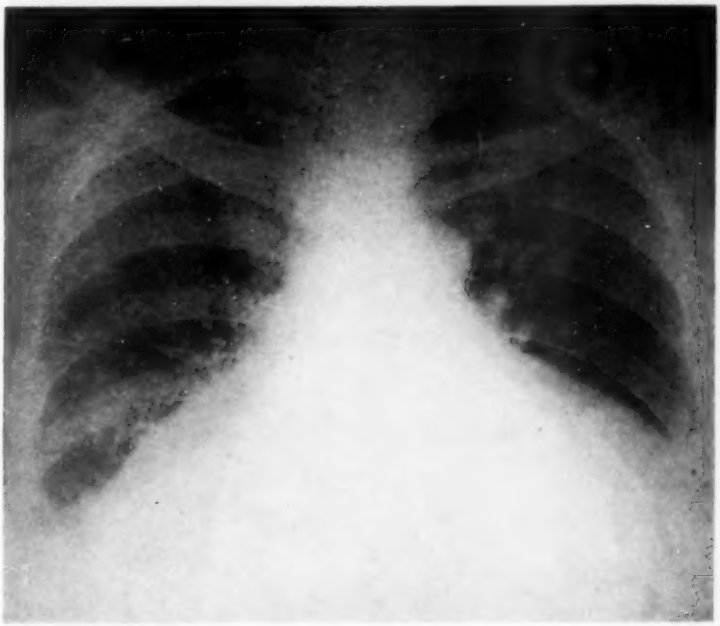

FIG. 1a. Roentgenogram of chest, October 30, 1950 (case 2).

tomatic. There has been no apparent recurrence of pericardial effusion while she is being maintained on thyroid extract, 180 mg. daily.

Case 2. The second patient was a 54 year old Negro female (table 2), first seen in the Vanderbilt Clinic in October, 1951, complaining of loss of taste of two months' duration. Hysterectomy for fibromyomata had been done in 1931. Blood pressure had been known to be elevated since 1943, at which time, over a period of several months, there had been a weight gain of 24 pounds, increased sensitivity to cold, and dyspnea on walking four or five blocks. In 1946 her basal metabolic rate was discovered to be minus 28 per cent. In 1948 she was hospitalized at another hospital for hypertension of 200/110 mm. of Hg. Chest film at that time showed enlargement of the cardiac shadow suggestive of pericardial effusion. Mercuhydrin injections for increasing dyspnea failed to effect a diuresis. In 1950 slight temporary right-

sided weakness developed, with some residual slurring of speech and memory defect. Also, in 1950, exertional dyspnea which had been present for two years was improved by digitalization.

In October, 1951, following a routine chest film which showed an enlarged cardiac shadow suggestive of pericardial effusion (figure 1a), she was admitted to Presbyterian Hospital for studies.

Physical examination revealed a thin female in no distress, afebrile and not dyspneic. Her skin was dry and scaling. Speech was slow, and no hoarseness was present. Hair was thin, spotty and moderately coarse. Mucous membranes of the

FIG. 1b. Roentgenogram of chest, December 14, 1951 (case 2), after pericardial paracentesis and instillation of 75 c.c. of air into pericardial cavity.

conjunctivae and mouth were pale. Fundi showed grade II changes in arterioles without hemorrhages or exudates. Tongue was grossly normal, although no taste appreciation was present. There was no venous distention, and the thyroid was not palpable. Examination of the chest revealed dullness at the right base posteriorly, with decreased tactile fremitus, voice and breath sounds, and crackling râles over this area. Dullness was present over the left anterior chest and extended to the left axilla, with absent breath sounds. The left border of cardiac dullness extended to the midaxillary line in the fifth left intercostal space. Forceful point of maximal impulse was present 10 cm. from the midsternal line in the fifth left intercostal space. Rate was 64, and regular. A_2 was greater than P_2, and no murmurs were heard. Blood pressure was 220/110 mm. of Hg in both arms. The liver was palpable 3 cm.

below the right costal margin, and there was no ascites. No ankle edema was present, and ankle jerks relaxed sluggishly.

Laboratory data revealed hemoglobin, 11.5 gm. per cent; hematocrit, 37 per cent; erythrocyte sedimentation rate, 53 mm. in one hour; white blood cell count and differential, normal. Wintrobe indices were MCV, 81 $cu\mu$; MCH, 24.5$\gamma\gamma$; MCHC, 31 per cent. Fifty per cent phenolsulfonphthalein was excreted in two hours. Examination of the urine revealed 2 plus albumin. Blood urea nitrogen was 18 mg. per

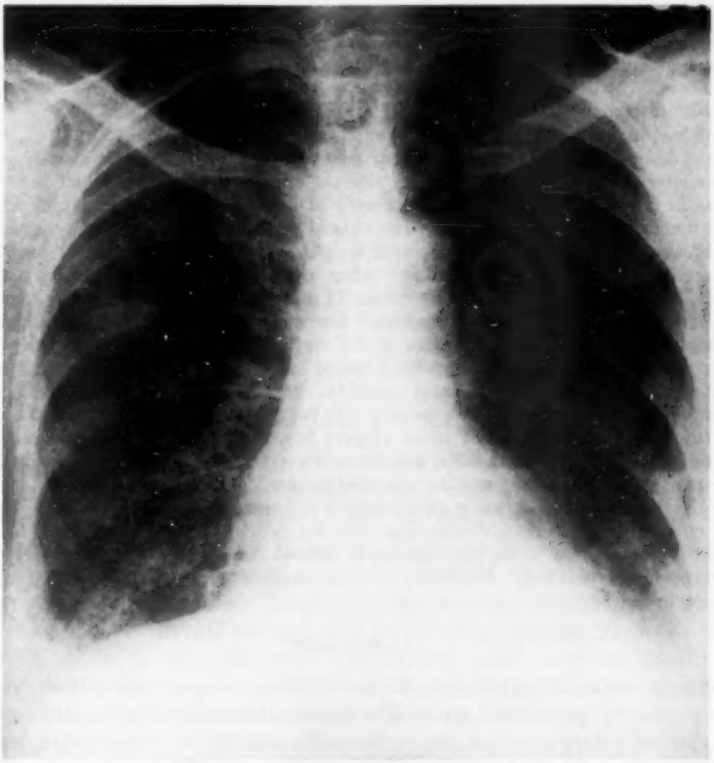

FIG. 1c. Roentgenogram of chest, June 13, 1952 (case 2), after eight weeks of continuous thyroxin therapy.

cent, and fasting blood sugar was 70 mg. per cent. Chest film showed the transverse diameter of the heart to be 22 cm., with the internal transthoracic diameter 25.8 cm. Considerable fluid was present in the right costophrenic sinus. Electrocardiogram showed low T-waves throughout and inverted T_3, T_4 and TaVF. Venous pressure measured in the antecubital vein was 100 mm. of saline. Circulation time (arm-to-tongue) with Decholin was 18 seconds. Mazzini test was negative.

Serum cholesterol was 290 mg. per cent, with 70 per cent esters. Basal metabolic rate was minus 21 per cent. Radioactive iodine uptake with 40 microcuries of radioactive iodine was 3 per cent uptake over the thyroid region in 24 hours.

Protein bound iodine was 1.2 gamma per cent, with normal range of 3.5 to 7.5 gamma per cent. Total serum proteins were 7.5 gm. per cent, with albumin of 4.3 gm. per cent, and globulin of 3.2 gm. per cent by the Howe method.

Pericardial paracentesis was performed, with removal of 250 c.c. of straw-colored fluid and instillation of 75 c.c. of air into the pericardium (figure 1b). This fluid showed a specific gravity of 1.024, with protein of 6 gm. per cent. Cell count showed 100 cells per cubic millimeter, with 40 per cent lymphocytes and 60 per cent red blood cells. Numerous crystals, flat and square, thought to be cholesterol crystals were present. Cholesterol determined on the centrifuged sediment was 100 mg. per cent. Electrophoretic pattern of the pericardial fluid * showed the following arbitrary area units: albumin, 270; alpha-1 globulin, 31; alpha-2 globulin, 28; beta-globulin, 34; gamma globulin, 90; fibrinogen, 21. Cell block and cultures were negative for tuberculosis.

Fluoroscopy performed immediately after the paracentesis showed forceful cardiac pulsations and a thin pericardium. The patient was started on 15 mg. of thyroid extract daily, with dosage doubled every two weeks. When she was discharged five weeks later she was taking 60 mg. of thyroid extract daily. There had been a decrease of 5.5 cm. in the transverse diameter of the heart by roentgenogram, and the basal metabolic rate was minus 6. The patient seemed brighter and more active, but she became unhappy over the 15 pound weight loss which had occurred on thyroid extract and discontinued medication. After cessation of thyroid therapy for two weeks, her basal metabolic rate was minus 23 per cent; cholesterol, 331 mg. per cent; protein bound iodine, 2.0 gamma per cent. She was then started on 1-sodium thyroxin, 0.1 mg. daily, with weekly increases of 0.1 mg. until she was taking 0.3 mg. daily. After five weeks of thyroxin, the protein bound iodine was 5.5 gamma per cent; serum cholesterol, 283 mg. per cent; basal metabolic rate, minus 15 per cent. A chest film taken eight weeks after thyroxin therapy was begun showed a reduction of 3.2 cm. in the transverse diameter of the heart (figure 1c). After eight weeks the supply of thyroxin was no longer available, and thyroid extract, 60 mg. daily, was substituted. The patient has continued to take this medication for 10 months.

Her basal metabolic rate is now minus 3 per cent, the left border of the heart is just outside the left midclavicular line, and the heart sounds are forceful. No evidence of enlargement of the liver, edema or pleural fluid is present. Ankle jerks now show prompt relaxation. Erythrocyte sedimentation rate has remained elevated at 62 mm. in one hour.

Discussion

The presence of pericardial effusion in these two patients with myxedema was proved by pericardial tap. The manifestations of "right-sided failure," the marked enlargement of the cardiac silhouette by roentgenogram, and the electrocardiographic changes in both cases reverted towards normal with the disappearance of the pericardial effusion on thyroid therapy. These changes suggest that the pericardial effusion played a major rôle in the production of the cardiac dysfunction.

Evidence for this interpretation is afforded by the case records in the literature of myxedema associated with pericardial effusion, proved either by pericardial paracentesis or at autopsy [5, 8, 10, 12-24] (table 3). Of the 44 cases reported, 32 have sufficient data to allow comment, and of these, two

* These analyses were kindly carried out by Dr. Dan H. Moore, of the College of Physicians and Surgeons, Columbia University, New York.

TABLE III

Analysis of Clinical Findings in Patients with Myxedema Associated with Pericardial Effusion

	Range	Number of Cases	Number of Cases Allowing Comment
Age	24 to 69 yrs.		
Between 50 and 70 years		22	31
Sex			
Male		4	
Female		28	
Duration of symptoms	6 wks. to 24 yrs.		
3 years or more		21	27
Pulmonary congestion		0	29
Right-sided failure		11	27
Associated ascites and/or pleural effusion		13	25
Basal metabolic rate	−3% to −69%		
Lower than −30%		15	26
Serum cholesterol	155 mg.% to 680 mg.%		
Greater than 300 mg.%		11	22
Pericardial fluid			
Amount (by paracentesis)	8 c.c. to 1600 c.c.		
(at autopsy)	1000 c.c. to 4000 c.c.		
Specific gravity	1.012 to 1.030		
Greater than 1.015		8	9
Total proteins	1.8% to 6.7%		
Greater than 4.0%		16	21
Cholesterol	45 mg.% to 187 mg.%		
Heart size normal during therapy	10 days to 9 months		13
Maximal decrease in heart size	2.0 cm. to 10.3 cm.		

were established at autopsy. In the two cases proved at autopsy, pericardial effusions of considerable size (1 and 4 L.) were found. The heart size was described as normal in both cases. Of the 30 patients followed clinically, pericardial effusion was known to be present for as long as four, five and 16 years in three cases,[25, 15, 23] and for five and probably three years in the two cases reported here. In all 32 cases, cardiac abnormalities reverted toward normal on thyroid therapy in a period ranging from 10 days to nine months. It is unlikely that this consistently good response to thyroid therapy would have been observed if significant cardiac dilatation and hypertrophy or myocardial fibrosis had been present.

Recently Kern et al.[21] demonstrated the presence of pericardial effusion in four successive cases of myxedema, two of which had relatively little enlargement of the cardiac shadow. These authors concluded that "pericardial effusion is a constant, early and major factor in so-called 'myxedema heart.'" Although there was evidence of right-sided failure in 11 of 27 cases (table 3), in none of the cases reported in the literature or in the two cases reported here was pulmonary congestion present. If the cardiac enlargement noted in the cases of "myxedema heart" was due to significant cardiac dilatation rather than pericardial effusion, one would expect some incidence of pulmonary congestion in these cases. Further, digitalis was of little or no therapeutic value.

It is well recognized that the abrupt administration of large doses of thyroid extract in the treatment of myxedema may precipitate coronary insufficiency or congestive failure.[8, 25] This is probably due to the sudden increase in cardiac output by a heart adjusted to a low output,[26, 27] resulting from decreased demands for oxygen in the prolonged hypothyroid state. The presence of pericardial effusion would also contribute to decreasing cardiac output.

The pathologic data on the heart in myxedema which have been reported [9-12] describe, in addition to the pericardial effusion, nonspecific changes in the myocardium such as degeneration of muscle fibrils, vacuolization and interstitial edema. The frequency of these myocardial changes is difficult to ascertain in view of the paucity of autopsy material. However, the present discussion does not preclude a rôle of interstitial edema in the production of "myxedema heart."

In the 25 cases of myxedema with pericardial effusion in which there are sufficient data for comment, 13 had associated pleural or peritoneal effusion or both. In addition to this clinical experience, pericardial as well as other serous cavity effusions have been observed in myxedema induced by thyroidectomy in rabbits, sheep and goats.[40] The mechanism of the production of effusions into serous cavities and of interstitial edema in hypothyroidism is not well understood. It is unlikely that these phenomena are due primarily to myocardial insufficiency, in view of the improvement with the administration of thyroid extract alone. Also, it seems improbable that these changes can be attributed to renal retention of salt and water, since Davies [37] has demonstrated, in patients with myxedema, that despite a decrease in glomerular filtration rate the capacity to excrete salt and water is normal.

A possible mechanism to explain the interstitial accumulation of fluid in myxedema is increased capillary permeability. Lange,[41] using a photofluorescein method, has demonstrated increased capillary permeability in patients with myxedema which reverts to normal on therapy with thyroid hormone. The high protein content of the effusions is compatible with this hypothesis. It is possible that fluid retention in myxedema may result from the interstitial elaboration and accumulation of hydrophilic substances. Indeed, Watson and Pearce [42] have presented histochemical and chemical evidence of an interstitial accumulation of hydrophilic polysaccharides in localized myxedema.

Although one can only speculate regarding the mechanism of production of the pericardial effusion in myxedema at this time, it seems most likely that pericardial effusion plays a frequent and important rôle in the genesis of cardiac symptoms and signs associated with myxedema. It should be stressed that, in patients with long standing and recurrent pericardial effusions, the diagnosis of myxedema must receive serious consideration.

Summary

1. A report is presented of two cases of myxedema associated with cardiac abnormalities in which the cardiac symptoms and signs were attributable to the presence of long standing and massive pericardial effusion, proved by pericardial paracentesis.

2. Case reports of "myxedema heart" with proved pericardial effusions are reviewed. Clinical evidence is cited which strongly suggests that pericardial effusion is of frequent occurrence and an important factor in accounting for the cardiac dysfunction in "myxedema heart."

Acknowledgment

The authors wish to express appreciation to Dr. Paul Wermer for suggesting the possibility of myxedema in case 1.

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THE MANAGEMENT OF UPPER GASTRO-INTESTINAL HEMORRHAGE *

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THE more frequent occurrence of upper gastrointestinal bleeding during the past decade has produced a great many papers on the management of this emergency. There have been and still are many proponents of pure, conservative medical management of these patients. Likewise, our surgical colleagues have enthusiastically plied us with statistics apparently showing the superiority of surgical treatment, supplemented by such slogans as "eventually, why not now." Yet both means of therapy have resulted in mortality rates for bleeding peptic ulcer which usually exceed 5 per cent, the maximum acceptable today. It may well be true that in unusual instances a routine surgical approach may be best for the patient. Conversely, the small community hospital lacking a trained anesthetist, blood bank, radiologist and skilled surgeon will save more lives if its staff concentrates on the conservative feeding regimens of the 1930's. Our thesis, however, is aimed at the vast majority of hospitals, wherein is available a well trained staff of internist, surgeon, clinical pathologist and radiologist, supported by an adequate blood bank and operating room personnel. We feel that a team of these doctors, aware of the varied problems in management of gastrointestinal bleeding and trained in the necessary procedures to save life, can reduce fatalities from bleeding peptic ulcer to less than 2 per cent, and, perhaps more strikingly, save the individual with an unusual source of his bleeding. Such a team can select, early in the course of the bleeding episode, those patients who will continue to hemorrhage or who will be apt to bleed again in a few hours. A few of these patients would die if medical therapy were continued, yet if operated upon early the surgical mortality will be that of elective gastrectomy, approximately 2 per cent. Crohn [1] has recently written a superb review of the need for aggressive therapy in the care of these patients.

A team for management of gastrointestinal bleeding was organized at the West Roxbury Veterans Administration Hospital in July, 1946, and has continued in operation since that date. We published preliminary observations [2] after two and one-half years, and will review the results of five years' experience now. Such a review clarifies our thesis more effectively than drab statistics alone. Our hospital population being largely males, it is not surprising that 462 (1.2 per cent) of the 29,206 patients

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From Veterans Administration Hospital, Boston, Massachusetts.

admitted during this period entered for treatment of upper gastrointestinal tract bleeding. Of these, 246 were found to fall within the general criteria of having had a "massive" or "severe" hemorrhage, viz., a fall in red blood cell count to 3 million or less, the hemoglobin to below 8.0 gm. per 100 c.c., or a state of blood volume insufficiency requiring the immediate replacement of at least 1,000 c.c. of blood. Our figures will henceforth refer only to this massive bleeding group. It is only by this restriction, and the inclusion of all patients dying immediately or remotely as the result of or related to bleeding, that an honest appraisal of results can be made. We have averaged nearly one severe bleeder a week, although, in fact, the patients tended to bunch up during the "bleeding seasons"—usually the months of October and November, and February, March and April.

Table 1 reveals our experience with bleeding due to peptic ulcer. Six of 184 ulcer patients died, producing a gross mortality of 3.2 per cent. Only one third of these patients were over 50 years of age. Of the 161 patients

TABLE I

Causes of Massive Bleeding
1946–1951

Diagnosis	Number of Patients	Deaths
Peptic ulcer	184	6
Duodenal ulcer	161	2
Gastric ulcer	20	4
Marginal ulcer	3	0
Esophageal varices	20	16
Gastritis	13	0
Miscellaneous*	4	2
Source unknown	25	0

* Carcinoma, benign tumor, cirsoid aneurysm, uremia.

with a duodenal ulcer, two died; one arrived at the hospital in a moribund condition and died within five minutes; the second died of myocardial rupture secondary to massive myocardial infarction occurring on the fourth day after apparent cessation of bleeding and at a time when his hemoglobin had been stabilized at 12.6 gm. per 100 c.c. Unfortunate occurrences similar to the latter patient are usually not preventable and will crop up periodically. Four of 20 patients with gastric ulcer died, two exsanguinating without operation within 12 hours of admission, a third dying shortly after operation which had unwisely been postponed for three days, during which time he had been transfused with 13 liters of blood. These deaths, occurring early in our study, convinced us that a bleeding gastric ulcer usually constituted a graver and more serious hazard than a duodenal ulcer. In the five years, 32 emergency or urgent operations (17 per cent) were performed with the single death mentioned above (an operative mortality rate of 3 per cent).

In reviewing our experience with the less common (25 per cent) causes of bleeding, the most striking finding is the very poor prognosis of severe bleeding in patients with esophageal varices and cirrhosis of the liver. This

will be discussed in detail later. It is important to consider this fatality rate and the newer surgical methods of therapy for bleeding varices, both of which demonstrate the importance of early diagnosis of the source of hemorrhage. Bleeding from gastritis can be very severe on occasion, but not as a rule. One patient exsanguinated in the late stages of a previously recognized carcinoma of the stomach, and one patient with uremia and nephrosclerosis had a massive terminal hemorrhage the source of which could not be determined at autopsy.

Management

All patients with gastrointestinal hemorrhage are admitted to the Medical Service, but our surgical colleagues are promptly notified of such admission and see each patient with us within four hours. Our interests are directed toward five spheres: (1) treatment of shock and restoration of adequate circulating blood volume; (2) medical control of bleeding; (3) investigation of the source of bleeding; (4) study of the patient for evidence of significant complications, including systems other than the gastrointestinal tract, and (5) estimation of rate and manner of bleeding.

An infusion of 5 per cent glucose in normal saline is promptly begun and the patient's blood cross-matched. It has been recognized for many years that hematemesis is one of the cardinal symptoms of the truly major hemorrhages. If this symptom is present, and red rather than tarry stools are passed, one can safely assume that one or more liters of blood have been lost and plan replacement accordingly. We believe that blood transfusions are the essential backbone of therapy and should be administered as soon as cross-matching can be performed and at a speed and volume necessary to maintain the hemoglobin above 10 gm. per 100 c.c. and the red cell count above 3.5 million. This insures an adequate blood volume reserve so that, should bleeding recur, irreversible shock will not appear. The pulse, blood pressure, stools, vomitus and transfusions are all charted together to present a complete graphic picture of the patient's course.

It has often been demonstrated that a program of feeding is very effective in the moderately bleeding ulcer patient, and such a routine should be followed, since 75 per cent of all bleeders have ulcers. However, the patient who is vomiting frequently will not retain food. As the blood in his stomach is a good buffering agent and he is apt to be a surgical candidate, we withhold food until several hours have elapsed since the last hematemesis. We then feed small amounts of milk, Jello or custard hourly, day and night, and in the proved ulcer patient add calcium carbonate, with or without magnesium oxide, between feedings. Aluminum hydroxide gel and magnesium trisilicate are so apt to produce severe fecal impactions that they are best omitted until bleeding has ceased, when they can be substituted for the calcium carbonate. Vitamins C and K are arbitrarily and not too scientifically employed in large doses in the initial intravenous solution and daily there-

after. Sedation of the ulcer bleeder, except the elderly, must be effective and is best accomplished by combinations of parenteral Demerol and sodium luminal alternating every four or six hours. Morphine is too apt to evoke vomiting and need rarely be used. The patient with cirrhosis should of course receive only a small initial dose of sedative. Atropine in 0.7 mg. doses is injected subcutaneously every six hours in the young ulcer bleeder. It should not be administered in the elderly or the alcoholic, as it is very apt to initiate a toxic psychosis in the latter. Buffered thrombin is recommended only for patients with gastritis, or if other measures have not been effectual in stopping ulcer bleeding. We have used this therapy in over 25

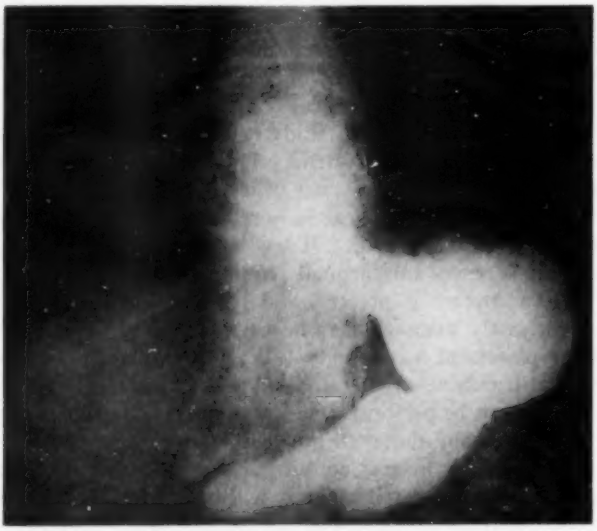

FIG. 1*a*. Gastrointestinal roentgenogram of patient showing large hiatus hernia demonstrated at an earlier bleeding episode.

patients and have not been impressed with a frequent coincidental cessation of hemorrhage.

The determination of the source of hemorrhage has become increasingly important now that effective surgical treatment is available not only for the ulcer patient but also for the control of the esophageal varix bleeder. The history must be carefully sifted for previous ulcer symptoms, and a history of alcoholism or jaundice cannot be taken lightly. The physical examination, if normal except for epigastric tenderness, suggests ulcer, but the presence of a large liver and numerous spider telangiectases does not rule out the presence of an ulcer—in fact, 16 per cent of our cirrhotics had peptic ulcer as well. To our surprise and dismay, we found that our ability to diagnose clinically the source of bleeding in the older age groups was less

than 70 per cent accurate. Since these are the patients in whom our special interest lies, we resorted to the emergency gastrointestinal x-ray examination of Hampton, as modified by Schatzki.[8] Between 1946 and 1949 we employed this maneuver only when the patient had continued to bleed for 36 to 48 hours. As a result of this policy three patients with gastric ulcer died needlessly, from frank exsanguination. One example in particular made us change: A 64 year old mechanic had been studied at this hospital in 1948 for a severe anemia which was found to be associated with guaiac-positive stools. A large hiatus hernia (figure 1*a*) was found by x-ray examination. Some months later an episode of hematemesis occurred and x-rays at another

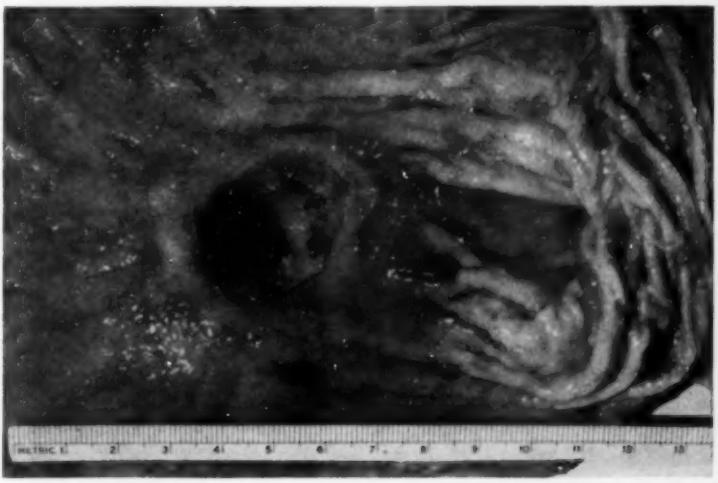

FIG. 1*b*. The large gastric ulcer and multiple eroded vessels at the neck of the herniated portion of the stomach found at autopsy after exsanguination.

hospital again revealed only the hiatus hernia. His final admission was preceded by 24 hours of repeated hematemesis and melena. He was in shock on arrival in the midafternoon, but two liters of blood effected normal circulation by 7:00 p.m. Although we felt his bleeding had been unusually profuse for gastritis in a hiatus hernia, it was decided to carry him over the night on conservative therapy. Four hours later bleeding recurred and, despite four simultaneous transfusions under pressure, blood poured from mouth and anus and death ensued in less than an hour. Post mortem revealed a 3 by 3 cm. gastric ulcer (figure 1*b*) at the neck of the hernia, in the base of which were four large eroded vessels. This death—entirely preventable, as are all exsanguinations—made us change our policy. We now hold to a program of emergency gastrointestinal x-ray examination of all patients over 40 years of age as soon as they have been brought out of shock,

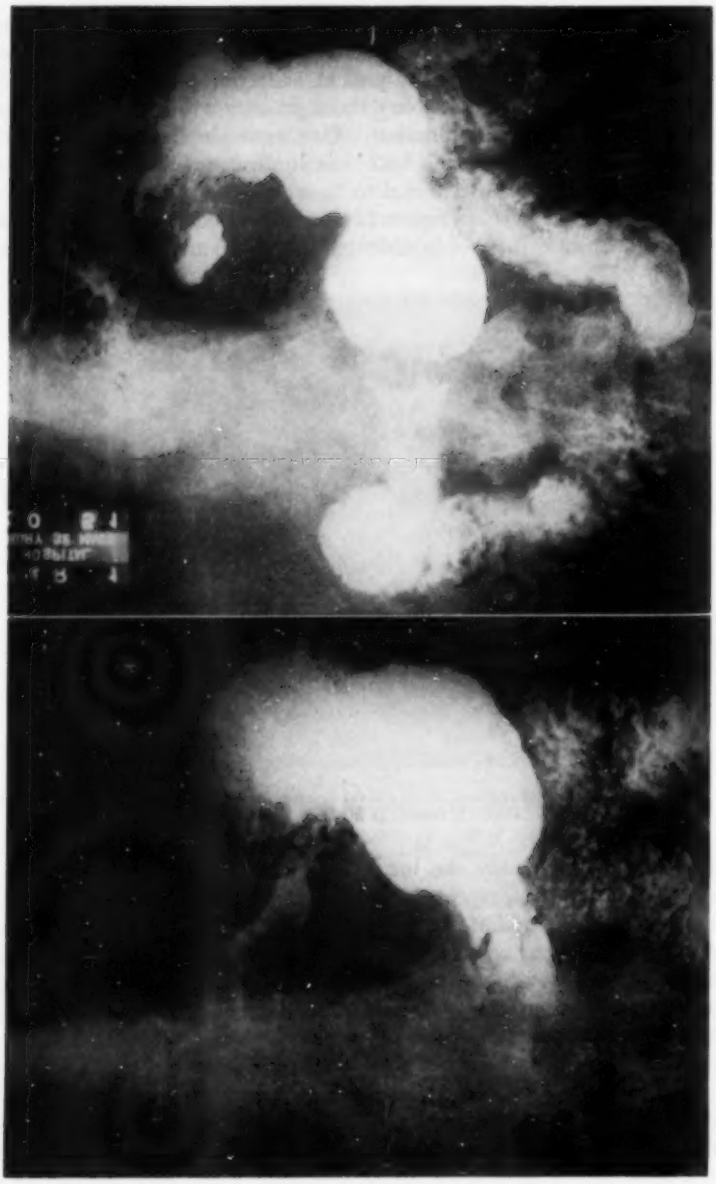

FIG. 1c. Roentgenograms of emergency gastrointestinal series in a second patient, demonstrating a similar gastric ulcer in the neck of the hernia immediately prior to successful operation.

and regardless of previously diagnosed gastrointestinal lesions. The films are then reviewed by all members of the team. Not long after establishing this routine, a situation very similar to that of the above patient appeared, but in this instance the emergency x-ray (figure 1*c*) clearly defined the lesion, and the proper incision and operation were readily performed by the surgeon, and the patient is well today. Between 1946 and 1951 we performed 100 gastrointestinal x-rays within the first 72 hours of admission. The results of these are given in table 2. In the last 18 months, 75 such examinations have been made within 12 hours of admission with equal freedom from renewal of bleeding so long as the patient is not in shock, is only turned and never heavily palpated. Inability to swallow is another contraindication to such examination. The results reflect to a large extent the radiologist's interest and his willingness to make a careful study under trying circumstances. Esophageal varices are well seen with Rugar barium, and we are unaware of ever having missed them when they were indeed the source of bleeding. Gastric ulcers are usually demonstrated best after a single swallow of Rugar barium which, being heavier than blood clot, slips around on the

TABLE II

Emergency Gastrointestinal Roentgen Examinations

1946–1951 (72 hours)	100 patients
1951–1953 (12 hours)	75 patients
No diagnosis established	28 (16%)
Incorrect diagnosis	24 (14%)
Procedure not completed	7 (4%)
Possible recurrent bleeding	5 (3%)

dependent surface of the stomach until the proper position is obtained, when it puddles amid the shadow contrast (figure 2). Duodenal ulcer craters are harder to demonstrate, but the deformity of the duodenal cap is easily seen. Our x-ray staff have now acquired such dexterity that in 15 per cent of the bleeders they can present us with two or three possible sources of bleeding, a situation suggestive of "The Sorcerer's Apprentice."

Another advantage of early roentgen examination is the reduction of the number of "unknown source of bleeding" patients by fully half—for us, from 15 per cent in the first three years of our study to 7 per cent during 1950 and 1951. We have repeatedly seen rapid healing of small gastric or duodenal ulcers (figure 3) within 12 days. We agree with Zamcheck [4] that early x-ray examination of the shockfree patient is thoroughly safe and, in interested hands, a most valuable aid in diagnosis of the origin of severe bleeding.

The development of the Sengstaken double balloon tube has also proved to be of great assistance in diagnosis as well as treatment. In our hands, when properly in position, it has always stopped massive bleeding from esophageal varices. We use it immediately in the cirrhotic with exsanguinating hematemesis, where its insertion may be followed by cessation of bleeding, indicating varices as the source. This procedure is much simpler

than esophagoscopy, which we now feel is unnecessary. Conversely, when two sources of bleeding are possible, e.g., esophageal varices and peptic ulcer, we will pass the tube and inflate both balloons. If bleeding persists, and the balloons are confirmed by x-ray to be in proper position, we then have presumptive evidence that bleeding is coming from the ulcer and not the varices. Barium can also be introduced into the stomach via the tube and an ulcer demonstrated, if x-rays have not already been made.

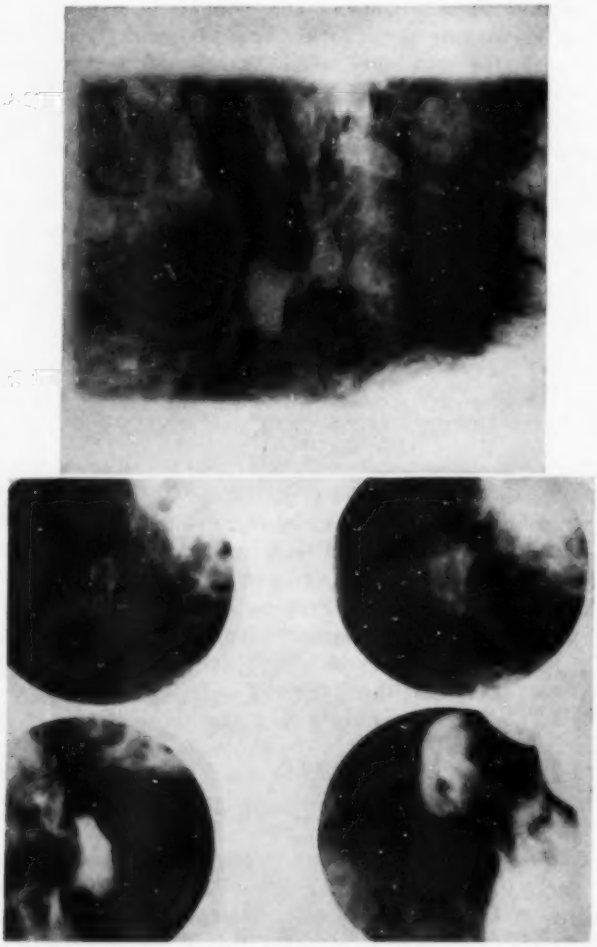

FIG. 2. Spot roentgenograms of a large bleeding gastric ulcer at the angle of the stomach, clearly outlined after a single swallow of barium. Twelve hours earlier an examination using routine amounts of barium had failed to demonstrate the lesion.

If melena alone has been present, and no source of bleeding found by emergency x-ray examination, passing a soft tube into the stomach and duodenum and aspirating the contents has proved of aid in establishing the presence of a lesion below the ligament of Treitz. The existence of a tumor of the small intestine must then be brought to mind.

The significant information about those patients likely to fare badly can best be obtained from an analysis of the patients who died or who required

TABLE III

Diagnosis	Age	Need for Operation
Emergency Operations		
*Gastric ulcer	26	Exsanguination and portal hypertension
Gastric ulcer	57	Exsanguination
Gastric ulcer	58	Exsanguination, perforation, coronary lesion
Gastric ulcer	64	Exsanguination
Duodenal ulcer	44	Exsanguination
Duodenal ulcer	57	Exsanguination
Duodenal ulcer	62	Rheumatic and coronary heart disease
Duodenal ulcer	63	Exsanguination, chronic pyelonephritis
Duodenal ulcer (2nd portion)	26	Exsanguination
Duodenal ulcer	35	Exsanguination, schizophrenia
Duodenal ulcer (2nd portion)	49	Exsanguination
Gastritis	36	Exsanguination
Urgent Operations		
Gastric ulcer	53	Hemorrhage, penetration
Gastric ulcer	42	Hemorrhage
Gastric ulcer	53	Hemorrhage
Gastric ulcer	53	Hemorrhage, schizophrenia
Gastric ulcer	42	Hemorrhage
Gastric polyp	25	Hemorrhage, recurrent
Duodenal ulcer	38	Hemorrhage, recurrent
Duodenal ulcer	58	Hemorrhage, arteriosclerosis
Duodenal ulcer	60	Hemorrhage
Duodenal ulcer (2nd portion)	26	Hemorrhage
Duodenal ulcer (2nd portion)	31	Hemorrhage
Duodenal ulcer	55	Hemorrhage, cirrhosis
Duodenal ulcer	60	Hemorrhage
Duodenal ulcer	39	Hemorrhage
Duodenal ulcer	40	Hemorrhage, penetration
Duodenal ulcer	49	Hemorrhage, penetration
Duodenal ulcer	60	Hemorrhage, cholecystitis
Duodenal ulcer	57	Hemorrhage, penetration
Duodenal ulcer	56	Hemorrhage, diabetes
Causes undetermined	52	Hemorrhage

* Died.

emergency surgery. We have already discussed the former. Table 3 briefly indicates the source of bleeding of the 12 patients in whom an emergency operation was performed to halt exsanguination, and 20 instances where it was performed on an urgent basis. Only one of these 32 patients died. It is apparent that one-half of the patients with gastric ulcers either died or had an emergency operation. Also, it is apparent that patients with duodenal ulcer plus some complication such as age, cardiovascular disease, hepatic or personality disorders, or local abnormalities, may be seriously jeopardized by massive bleeding, and are safely controlled by surgery. The internist

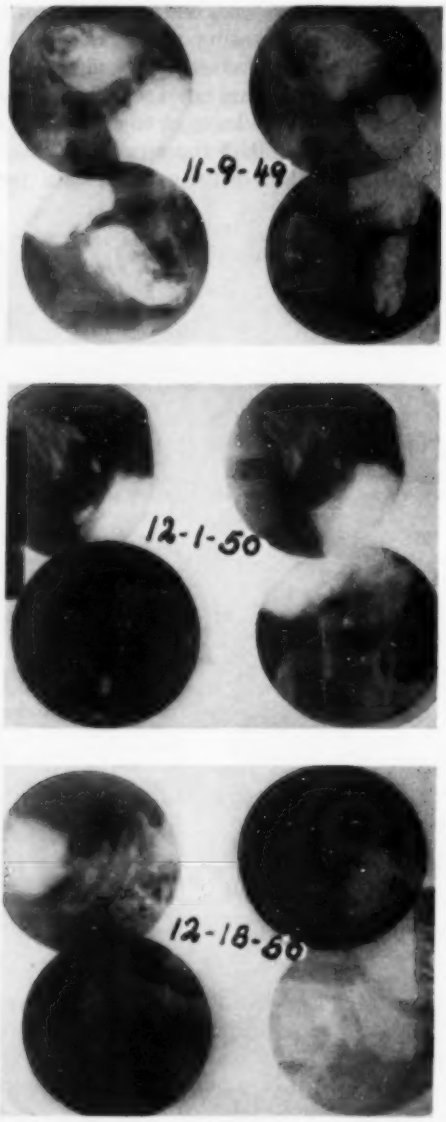

FIG. 3. Spot roentgenograms of the pyloric cap: (a) taken 12 days after a bleeding episode in late October, 1949, with a normal pylorus; (b) taken one day after admission in December, 1950, for another hemorrhage, and clearly depicting a large ulcer crater; (c) taken 18 days later, showing that the large ulcer niche has disappeared.

again plays a major rôle by quickly determining the presence of such complications from the history and physical examination, plus certain minimal laboratory tests: urinalysis for diabetes or nephritis, the blood smear for abnormal white cells or insufficient platelets, the prothrombin time and bromsulfalein test for hepatic function, the electrocardiogram for evidence of cardiac disease, and the chest roentgenogram for evidence of tuberculosis or tumors. Most of these determinations can be made, while the patient is being brought out of shock, so that important recommendations can be made to the other team members upon completion of the emergency gastrointestinal x-rays. Heart disease is not a contraindication but, rather, an indication for early surgery. Ulcers located beyond the duodenal bulb, so-called second portion or postbulbar ulcers, are particularly apt to involve the posterior duodenopancreatic artery, with the increased rate of bleeding found in the arterial spurter. We consider the finding of such an ulcer on x-ray to be second to gastric ulcer as an accessory indication for early operation. Age in itself is not a stimulant for early surgery, but the vascular problems so frequently accompanying this involution are. The finding of vascular insufficiency of any major organ prompts us toward operation.

We also believe that if no source for bleeding has been found by our various examinations, and the hemorrhage continues at a rate of over 3 L. of blood a day for more than 48 hours, then further delay without operation is not justified. The operation should include both exploration of the gastrointestinal tract to determine the highest level of blood within the tract, and subtotal gastric resection. Superficial gastric erosions, particularly when associated with submucosal vessels or cirsoid aneurysms, cannot be found by the usual exploratory technics, yet most of us with an appreciable experience with upper gastrointestinal hemorrhage have witnessed the incredible sight of blood spurting from apparently normal mucous membrane. For this reason we have felt, as have others,[5] that resection should always be undertaken.

Operations for bleeding should be simplified as much as possible to decrease the risk.[6] It may be wiser, in difficult and inflamed duodenal ulcers, only to suture the ulcer area and perform an exclusion operation, returning six weeks later for a second stage attack on the gastroduodenal stump. While bleeding may recur in the interim, this can be handled by the surgeon with his attention focused on this single objective, his gastrojejunal anastomosis having been completed previously. Duodenal stump problems are simplified by such a policy and this technical hazard is controlled.

Massive hemorrhage from esophageal varices associated with Laennec's cirrhosis has had an extremely high mortality rate (80 per cent) in our hands. Besides the severity of the bleeding, certain factors are worthy of comment. Ninety per cent of those who died were found at autopsy to have livers that were in the active fatty metamorphosis phase of the metabolic disorder that produces cirrhosis.

Obviously, a careful appraisal and scrutiny of our treatment of these patients are in order. Figure 4 reveals the results of three different types of therapy scattered over a six year period. It is immediately obvious that the mortality rates for the three are essentially the same, and that exsanguination was common in 1946 to 1948, but has been uncommon as the primary cause of death since then. The first group received a little blood replacement and an ulcer feeding program. In 1949 and 1950 more blood was provided, sedation was omitted, and the antibiotics penicillin and streptomycin were injected. During 1951 and 1952, a policy of early diagnosis of esophageal varices by x-ray with tamponade of the bleeding by the Sengstaken double

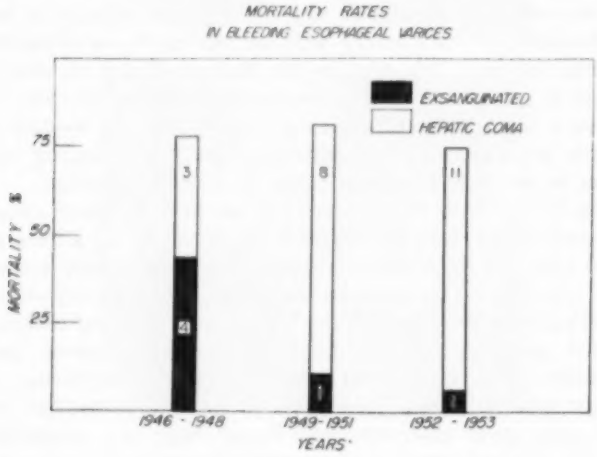

FIG. 4.

balloon tube plus blood replacement and antibiotics was carried out, with equally unhappy results. The patients bled less but they continued to die, jaundiced, comatose or delirious, with high temperatures, pulmonary edema and the above mentioned greasy livers at autopsy. At the present time we are embarked on a program of immediate tamponage, followed by surgical ligation of the varices at the first evidence of bleeding after deflation of the balloons, and large doses (up to 800 mg. per day) of cortisone. The latter has been thought by some to be life-saving in severe infectious hepatitis. Our current experience is encouraging. This new plan of therapy again underscores the importance of the team approach to this problem.

SUMMARY AND CONCLUSIONS

1. We have related our experience with 246 patients admitted for massive upper gastrointestinal tract hemorrhage treated by a team composed

of an internist, a surgeon and a radiologist. The mortality rate from bleeding peptic ulcer was 3.2 per cent.

2. Prompt restoration of circulating blood volume by blood transfusion was essential.

3. Early diagnosis of the source of the bleeding by emergency roentgen examination is necessary if an aggressive approach to bleeding is to be undertaken. It proved to be a safe procedure and an extremely valuable aid in diagnosis in interested and competent hands.

4. Gastric and postbulbar duodenal ulcers were noted to be prone to bleed uncontrollably and to become candidates for early surgery. Other systemic complications increase the hazard of ulcer bleeding and point toward an early surgical intervention.

5. The management of bleeding from esophageal varices is becoming a potential surgical problem and adds another reason for the team approach to upper gastrointestinal bleeding.

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THE CLINICAL COURSE, FOLLOWING ADRENAL RESECTION AND SYMPATHECTOMY, OF 82 PATIENTS WITH SEVERE HYPERTENSION *

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Introduction

Previous reports of our testing of operations for hypertension, combining adrenal resection with sympathectomy, have indicated encouraging results.[1, 2, 3, 4] The number of patients so treated has increased steadily. We now feel it in order to present a progress report concerning 82 patients who were operated upon prior to December 31, 1952.

It does not seem necessary to review again the experimental and clinical evidence indicating the rôle of various adrenal hormones in homeostasis of the circulation, or in the maintenance of blood pressure levels in clinical hypertension.[2, 4, 5] Following Green's experience [6] of observing amelioration of severe hypertension and diabetes mellitus following adrenalectomy, we embarked on a study of the effects of subtotal adrenalectomy. Thorn and his associates [7] subsequently have explored the effects of total adrenalectomy. Our program was facilitated by the early availability of cortisone,† and by our having access to the knowledge and skills of many individuals in the Hospital and the School of Medicine of the University of Pennsylvania.

This report concerns 82 patients, followed for from one to 33 months after varying degrees of adrenal resection, performed with or without various types of sympathectomy. It is our impression at present that sympathectomy combined with adrenalectomy is more effective than either sympathectomy or adrenalectomy alone. Our subsequent observations can be expected to allow comparison between similar types of patients treated by sympathectomy alone, versus sympathectomy plus adrenal resection.

Types of Operations Performed

Figure 1 indicates the type of sympathectomy devised by Peet. It shows also the modifications of the Adson and Smithwick procedures which

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one of us (H. A. Z.) has performed in our patients. The modified Adson operation includes removal of the twelfth thoracic and the upper two lumbar sympathetic ganglia, together with interruption of the three splanchnic nerves. For the Smithwick type of sympathectomy, the lower six or seven thoracic ganglia and the three lumbar ganglia are removed, and the splanchnics are excised. With a few early exceptions, operations were performed through the subdiaphragmatic and retroperitoneal approach, in two operative stages about 10 days apart.

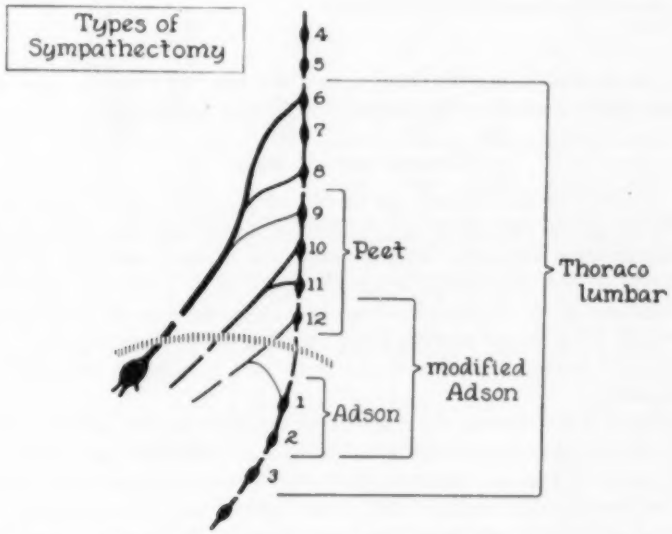

FIG. 1. Types of sympathectomy commonly employed for the treatment of hypertension. The so-called total sympathectomy of Grimson is not included in this diagram. For the Smithwick (thoracolumbar) sympathectomy, the lower six or seven thoracic ganglia and the three lumbar ganglia are removed, and the three splanchnic nerves are interrupted above the diaphragm. The modified Adson operation performed by one of us (H. A. Z.) includes removal of the twelfth thoracic and the upper two lumbar ganglia, together with interruption of the three splanchnic nerves. It is performed through a subdiaphragmatic, retroperitoneal approach, in two stages about 10 days apart.

After a trial of various types of adrenal resection in the first 10 patients operated upon, it was felt that sufficient tissue had been removed when a fragment, equivalent to a cube measuring 5 or 6 mm. on a side, remained adjacent to the adrenal vein on the left, and all of the right adrenal gland had been removed. This, then, is our meaning of "subtotal adrenalectomy" with respect to the majority of the patients who were subjected to combined subtotal adrenal resection and sympathectomy.

Table 1 lists the various types of operations performed on 82 patients prior to December 31, 1952. An additional nine patients were operated

TABLE I

Types of Operations Performed in 82 Patients. The nine patients listed on the extreme right have not been followed for sufficient time to become a part of this analysis.

Subtotal Adrenalectomy	
Alone (SA)	11
With Adson sympathectomy (SA–ADN)	43 + 2
With Smithwick sympathectomy (SA–SMK)	8
With Peet sympathectomy (SA–PEET)	1
With Adson sympathectomy on one side and Peet on the other (SA–MIXT)	4
Total Adrenalectomy	
Alone (TA)	2
With Adson sympathectomy (TA–ADN)	11 + 7
With Smithwick sympathectomy (TA–SMK)	2
Total	82

upon as indicated during the ensuing two and one-half months. No attempt has been made to analyze the course of the latter nine patients.

EVALUATION OF RESULTS

In an attempt to evaluate the results of operation upon blood pressure and the symptoms and signs of hypertensive cardiovascular disease, a tentative classification has been devised (table 2). Our experience in studying the effects of the Smithwick sympathectomy since 1939 led us to expect these various types of response and to anticipate that certain individuals would shift from one to another category with the passage of time. Careful and repeated postural blood pressure tests [8] are manifestly essential for this classification.

In figure 2 are charted the results now apparent among patients subjected to various combinations of sympathectomy and adrenalectomy, and adrenalectomy alone. The two patients upon whom total adrenalectomy alone was done had severe renal damage and, in the light of our subsequent experience, improvement would not have been anticipated. With other operations, it is too early to find definitive trends. The high mortality among those subjected to subtotal adrenalectomy alone reflects the advanced stage of the disease of the patients, who were among the earliest ones chosen for operation. Contrarily, the preliminary results are encouraging among eight patients subjected to the Smithwick sympathectomy and subtotal adrenalectomy, because six of these patients were severely ill, being in the Smithwick Group 4 category.[9] It will be noted in figure 2, and subsequently, that there are no patients in category D: i.e., there are at present no *living*

TABLE II

Schema for Classification of Result Following Operation

A—Excellent B—Fair C—Poor D—Failure

A. Blood pressures less than 150/100 lying and standing.
B. Blood pressures more than 150/100 lying, less than 150/100 standing.
C. Blood pressures essentially unchanged following operation. Improved symptoms and signs.
D. Blood pressures, signs and symptoms unchanged following operation.

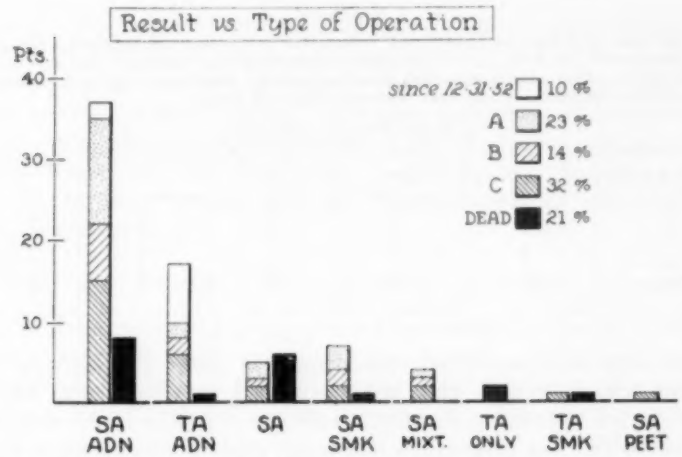

FIG. 2. Types of operations performed upon 91 severely hypertensive patients. Abbreviations as shown in table 1. Classification of result A, B and C, as defined in table 2. The majority of patients have been subjected to either subtotal or total adrenalectomy, combined with an Adson type sympathectomy. No surviving patients at present fall into the D, or failure, category. Twenty-three per cent have shown an excellent (A) result for periods of postoperative observation not exceeding 33 months. During the same period of time, 21 per cent of these severely hypertensive patients have failed to survive. The open blocks represent patients operated upon since January 1, 1953, who are listed, but not further analyzed, in this report.

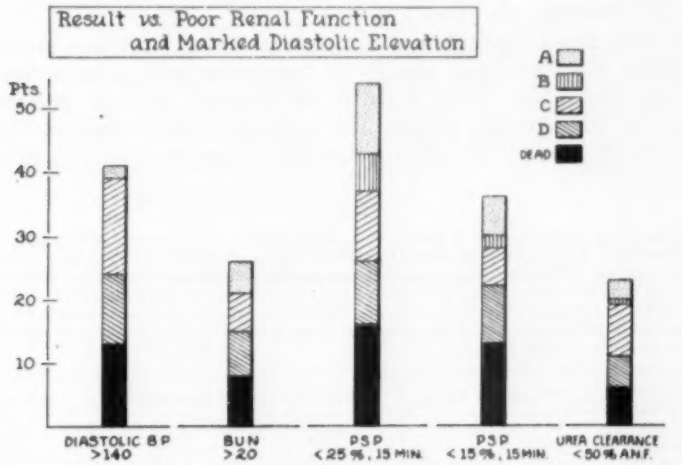

FIG. 3. Result obtained in patients with borderline renal function and marked elevations of diastolic blood pressure. An A (excellent) response was obtained in 10 patients who showed a phenolsulfonphthalein excretion of less than 25 per cent in the first 15 minutes after intravenous injection. Since there are currently no patients surviving in the D category of results, those shown as D in this chart are also shown in the "Dead" columns below.

TABLE III

Classification of Postoperative Result in Relation to Preoperative Smithwick Group. See table 2 for meaning of A, B, C, D. No patients have been operated upon who were in Smithwick Group 1. Poor results are most numerous among Smithwick Group 4 patients, but seven excellent results have also been observed from this group.

	Result Number of Patients				
Smithwick Group	A	B	C	D	Dead
1	0	0	0	0	0
2	8	5	8	0	0
3	6	4	5	0	2 (12%)
4	7	4	16	0	17 (39%)
Total	21	13	29	0	19

patients who have shown no improvement in either symptoms or signs. Patients who have died, even after apparently showing benefit following operation, are included in this analysis only as mortalities, save in figure 3.

Smithwick [9] has proposed a numerical grading system for evaluating the status of patients with severe hypertension. Because of inaccuracies which can arise in attempting to apply his criteria to a variety of patients, it should be regarded as a qualitative rather than a quantitative guide. Its usefulness is suggested (table 3) by the relatively poor results of our operations upon patients in whom his criteria suggest the poorest prognosis (Smithwick Group 4). Contrarily, it is of interest that seven of 48 patients, initially in Smithwick's Group 4, have shown an excellent (A) response at this stage following operation.

We have noted improvement in the eye grounds, heart size and electrocardiogram postoperatively, usually in association with a favorable effect upon blood pressure. Table 4 shows the incidence of such improvement. Among the 63 surviving patients the percentile improvement has been as follows: heart size, 41 per cent; funduscopic, 48 per cent; electrocardiogram,

TABLE IV

Incidence of Improvement in Heart Size, Retinopathy and Electrocardiographic Abnormalities in from 1 to 33 Months after Operation, among 63 Surviving Patients. See table 1 for abbreviations. The percentile improvement for those subjected to subtotal adrenalectomy and Adson type sympathectomy (SA–ADN) is similar to that of the total series. "Improvement" includes any persistent diminution in the heart's frontal area, any persistent decrease in the grade of retinopathy, and any progressive tendency for abnormalities of the QRS and T waves to revert toward normal.

Operative Procedure	Number of Patients	Heart Size	Funduscopic	Electrocardiogram
SA ALONE	5	40%	40%	40%
SA SMK	7	43%	70%	14%
SA ADN	35	43%	51%	30%
SA PEET	1	100%	100%	0
SA MIXT	4	75%	25%	75%
TA ADN	10	10%	20%	10%
TA SMK	1	100%	100%	0
Total	63	41%	48%	27%

27 per cent. As "improvement" we have included any persistent diminution in the frontal area of the heart, any persistent decrease in the grade of retinopathy, and any progressive tendency for abnormalities of the QRS and T waves to revert toward normal. The same proportion of improvement as for the entire series has been found among the 35 patients surviving after subtotal adrenalectomy and Adson type sympathectomy. As yet we have been unable to find consistent evidence of improvement in renal function following operation.[4]

Length of Survival and Follow-Up after Operation

In table 5 the duration of postoperative observation prior to this analysis, or prior to death, is listed for six month intervals. A relatively large number have been observed for not more than six months, and few have been followed for as long as 33 months.

Table V

Duration of Follow-up after Operation among 82 Patients

Time in Months	Number of Patients
0–6	32
7–12	16
13–18	12
19–24	17
25–33	5
Total	82

Since 44 (or over half) of our patients fall into Smithwick's Group 4, the loss of 19 of them within 33 months after operation was to be expected (table 6). An *operative* mortality of only 6 per cent, who died within a month of operation, seems creditable. The usual cause of death has been a cerebral vascular accident or coronary occlusion. Only one patient has died from adrenal insufficiency.

Table VI

Fatalities. Period of Survival Following Operation

Time in Months	Numbers of Patients
Less than 1	5
1 to 6	8
7 to 12	3
13 to 16	3
Total	19

Indications and Contraindications to Operation

We have deliberately chosen for operation severely hypertensive patients who have not responded to intensive medical treatment. Many of them have shown evidence of severe vascular damage involving organs other than

the kidneys. Our *tentative indications* for operation have been: (1) average diastolic blood pressures of 120 mm. of mercury or more; (2) failure to respond to intensive medical therapy [10, 11]; (3) evidence of progressive vascular damage. Tentative *contraindications* are: (1) poor renal function, with excretion of less than 20 per cent of phenolsulfonphthalein 15 minutes after intravenous injection, and/or a blood urea nitrogen of over 20 mg. per cent; (2) convalescence from a stroke or coronary occlusion for less than six months; (3) age of 55 years or more; (4) inability to coöperate with a careful follow-up program because of intellectual deficits or emotional instability. Some of these criteria are deserving of further comment in the light of our experience to date.

Coronary Artery Disease: It is our opinion that patients with known disease of the coronary arteries are poor risks for operation. We have not

TABLE VII

Occurrence of Angina Pectoris and Coronary Occlusion in Relation to Operation. Numbers of patients. Three patients having no history of angina prior to operation succumbed following a coronary occlusion after operation. Eight patients with rare attacks of angina preoperatively have had no angina since operation. Of the six patients with frequent anginal attacks prior to operation, two have been relieved of angina, two have survived coronary occlusions, and two have suffered fatal coronary occlusions.

Preoperative		Postoperative					
		Angina			Cor. Occlusion Recovery	Dead	
		None	Mild	Moderate		Cor. Oc.	Other Cause
No angina	3	0	0	0	0	3	0
Mild angina	8	0	0	0	0	0	0
Moderate angina	6	2	0	0	2	1	1

excluded these from our series, however, since we have anticipated that continued hypertension would aggravate damage to the coronary arteries as well as other vascular beds.

Contrarily, we were aware that such patients might not tolerate marked fluctuations in blood pressure after operation. Table 7 shows the clinical course of our patients who had angina pectoris or coronary occlusion either prior to operation or during a follow-up period not exceeding 33 months. It appears that *mild* angina may disappear following operation. Patients with more severe coronary disease have shown at best a variable course. It is our current practice to administer oxygen for 48 hours after each operative stage to patients with known coronary artery disease. Such patients are allowed to become ambulatory by more gradual stages than usual, particularly if a marked fall in blood pressure upon standing is observed after either operative stage.

Congestive Heart Failure; Paroxysmal Dyspnea: It became apparent

early in our study that a tendency toward heart failure was apt to be corrected following this type of operation.[4] This has been the subject of a separate report.[12] Table 8 illustrates the course of patients who have shown congestive failure or paroxysmal dyspnea prior to operation. Among them, 13 who had been in frank congestive failure and who have been followed postoperatively for more than one year now show the following: Only one has died (from adrenal insufficiency). Only two are now taking digitalis, at their own insistence and not because of persisting evidences of heart failure.

We have employed digitalis in those with congestive heart failure prior to operation. Following the first stage operation, intravenous solutions do not ordinarily include salt except for one pint of blood. After the second stage, physiologic salt solution comprises about one third of intravenous fluids given, and digitalis often can be discontinued.

TABLE VIII

Postoperative Course of 28 Patients in Relation to Preoperative Paroxysmal Dyspnea and Congestive Heart Failure. (See table 2 for definition of A, B, C.)

Preoperative	Postoperative				
	A	B	C	Dead	
				Heart Failure	Other Causes
Paroxysmal dyspnea 8	3	2	3	0	0
Frank heart failure 20	5	2	6	0	7

Renal Function; Degree of Hypertension: In the presence of severely impaired renal function, one of two courses postoperatively may be observed: (1) No change in blood pressure may occur. (2) The blood urea nitrogen may rise progressively, coincident with a clinical course which shows commensurate deterioration. Figure 3 illustrates the result of operation in certain patients whose renal function was borderline with respect to the tentative indications for operation stated above.

Marked elevations of the diastolic blood pressure appear per se to impose limitations upon the postoperative result (figure 3). This is in keeping with Smithwick's classification. When other complications were not present, we have generally elected to perform a more extensive Smithwick sympathectomy, in addition to adrenal resection, in the case of patients with diastolic blood pressures of 140 or more. Several such patients have presented complications, such as angina or a previous vascular accident, which have made us decide upon the more limited Adson type of sympathectomy.

Cerebral Vascular Damage: The course of patients who have had strokes prior to operation is indicated in table 9. It appears proper to continue to operate upon patients who have had a good recovery from cere-

TABLE IX

Postoperative Course of 14 Patients in Relation to Preoperative Cerebral Vascular Damage. (See table 2 for definition of A, B, C.)

Preoperative	Postoperative				
Stroke	A	B	C	Dead	
				Stroke	Other Causes
Without residuals 8	2	2	3	0	1
With residuals 6	1	1	2	0	2

bral vascular accidents for at least six months. Postoperatively, the same precautions have been observed as in those with coronary artery disease. An occasional patient who appears to have suffered intellectual impairment in association with severe hypertension has shown improvement postoperatively. Relief from headache due to hypertension is almost certain, as after a thoracolumbar sympathectomy alone. Hafkenschiel et al.[18] have calculated a decrease in cerebral vascular resistance, without a measurable diminution in cerebral blood flow or oxygen consumption, after these operations.

RESIDUAL ADRENAL FUNCTION

This preliminary analysis indicates that a favorable response to subtotal adrenalectomy, either alone or combined with sympathectomy, is infrequent unless sufficient adrenal tissue has been removed to render the patient susceptible to adrenal insufficiency when cortical replacement therapy and salt are withdrawn (table 10). Hills et al.[14] have made a quantitative estimation of residual adrenal function in 10 postoperative patients by a method developed for the purpose. The fact that a number of our patients have shown no evidence of appreciable cortical reserve following "subtotal" adrenalectomy has led us recently to increase our series of combined sympathectomy and total adrenalectomy (figure 2). From the standpoint of hemostasis at operation, it is simpler to remove all of an adrenal than to leave a small fragment adjacent to the adrenal vein.

TABLE X

Necessity for Adrenal Cortical Replacement Therapy Versus Postoperative Result among 63 Surviving Patients, and among 19 Prior to Death. Usual therapy includes cortisone, 12.5 to 25.0 mg. orally, 2 mg. DCA buccally, and enteric coated tablets of sodium chloride, 3.0 gm. daily. (See table 2 for definition of A, B, C.)

Replacement Therapy	A	B	C	Dead
Yes	18	10	22	16
No	3	3	7	3

During the first month after completion of operations, including extensive adrenal resection, a liberal amount of cortical replacement therapy has been given, if blood pressures are not more than an average of 180/100 mm. of Hg, or if there is the usual marked fall in blood pressure upon standing. This may include cortisone, 37.5 to 50 mg., in divided dosage daily, DCA, 2 mg. buccally, and enteric coated tablets of sodium chloride, 3 to 6 gm. daily. Subsequently, the dosage of cortisone, salt and DCA is diminished in each individual to achieve an optimal level of blood pressure but avoid anorexia, nausea or hyperkalemia. Larger amounts of these three agents are necessary during warm weather than in the cooler months. Patients are taught to report untoward symptoms promptly to their physicians, and to seek medical attention in the event of a respiratory infection or other febrile episode, in order that replacement therapy can be increased temporarily. With these precautions, no patient has required re-admission to the hospital for the treatment of acute adrenal insufficiency during the past 24 months.

Discussion

It is apparent that the operative approach to severe hypertension which we have chosen to follow is an attempt to combine the possible benefits of sympathectomy of the Adson and Smithwick types with subtotal or total adrenalectomy. The limited, Adson type sympathectomy, combined with adrenal resection and performed in two separate stages, has been well tolerated by most patients who have had adequate preservation of renal function. Patients so treated comprise the largest group in our series. Their convalescence has been marked by its ease, and freedom from the pulmonary complications and the prolonged backache which may follow thoracolumbar sympathectomy. Further observation is required to establish whether, or under what circumstances, this type of operation will prove superior in the long run to: (1) thoracolumbar sympathectomy; (2) thoracolumbar sympathectomy plus subtotal or total adrenalectomy, or (3) total adrenalectomy alone.[7]

Operations of this sort, on this type of patient, cannot be attempted without a well integrated medical and surgical team who are prepared to deal not only with all surgical complications, but also with any and all of the manifestations of severe hypertensive cardiovascular disease and adrenal insufficiency. A prolonged and careful follow-up is obligatory for each patient. Patients must be warned repeatedly that anorexia, nausea or vomiting means adrenal insufficiency and demands emergency treatment. They must also learn to report promptly to their physicians the occurrence of a cold or other febrile or infectious illness. During the summer months their requirements for cortisone, DCA and salt will be somewhat larger than during cool weather. A member of the team must be on call at all times, prepared to treat acute adrenal insufficiency or other emergency.

We have encountered to date no greater difficulty in managing patients following total adrenalectomy than following subtotal adrenalectomy. The majority of patients following an adequate "subtotal" resection have required cortical replacement therapy and have shown evidence of diminished adrenal cortical reserve. Such patients do not appear to lack energy and vigor for their full work load, barring cardiovascular complications. The only symptom frequently mentioned is a mild intolerance to cold.

Summary

1. A clinical report is presented of 82 severely hypertensive patients following various degrees of adrenal resection with and without various types of sympathectomy.

2. The *indications* for operation include three features: (a) an average diastolic blood pressure of 120 mm. Hg or more; (b) a failure to respond to intensive medical therapy; (c) evidences of progressive vascular damage.

3. Our tentative *contraindications* include any one of the following: (a) poor renal function, with excretion of less than 20 per cent of phenolsulfonphthalein 15 minutes after intravenous injection, and/or a blood urea nitrogen of over 20 mg. per cent; (b) convalescence from a stroke or coronary occlusion for less than six months; (c) age of 55 years or more; (d) inability, for any reason, to coöperate in taking adrenal cortical replacement therapy.

4. The majority (54) of patients have been subjected to an Adson type of sympathectomy, plus either subtotal or total adrenalectomy. In the case of subtotal adrenalectomy, all adrenal tissue is removed save a remnant about 6 mm. in diameter adjacent to the adrenal vein on the left side. These operations are performed through a subdiaphragmatic, retroperitoneal approach, in two stages about 10 days apart.

5. Further observations will be required to determine whether the Adson type of sympathectomy, combined with total or subtotal adrenalectomy, is more or less effective than (a) thoracolumbar sympathectomy, or (b) total adrenalectomy without sympathectomy.

6. During periods of postoperative observation of these 82 patients varying between one and 33 months, 23 per cent have shown an excellent response; in 14 per cent the response was fair; in 32 per cent, poor. Twenty-one per cent have failed to survive. Only one has died from uncomplicated adrenal insufficiency. The usual cause of death has been a stroke or a coronary occlusion. Those having paroxysmal dyspnea or congestive heart failure have shown the most striking improvement after operation. This appears to be primarily the result of extensive resections of adrenal cortex.

7. The majority of those subjected to subtotal adrenalectomy have required adrenal cortical replacement therapy postoperatively.

8. Objective changes have been observed among the 82 patients in the following respects: heart size reduced in 41 per cent; ocular fundi improved in 48 per cent; electrocardiogram less abnormal in 27 per cent.

9. The precautions necessary for the successful management of patients subjected to these procedures are discussed.

ACKNOWLEDGMENTS

Dr. William T. Fitts performed the operation of subtotal adrenalectomy in two of the cases included in this report.

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THE RELATIONSHIP OF CHRONIC ULCERATIVE COLITIS AND CIRRHOSIS *

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THE etiology of idiopathic ulcerative colitis is obscure; the same statement applies equally well to most types of human cirrhosis. The occurrence of two such diseases in the same patient raises the question, is there any possible relationship between the two disorders? The occurrence of cirrhosis and the existence of hepatic insufficiency in patients with chronic ulcerative colitis are by no means unknown. Comfort, Bargen and Morlock [1] in 1938 called attention to this association in a report of four cases. Tumen, Monaghan and Jobb [2] in 1947 described five patients who exhibited hepatic cirrhosis as a complication of chronic ulcerative colitis. The association of these two disorders was noted in a group of patients studied by Pollard and Block.[3] Data relating to the association of hepatic lesions and chronic ulcerative colitis have appeared in recent reports from the Mayo Clinic by Bargen and his associates.[4, 5, 6] Individual cases in which cirrhosis occurs as a complication of ulcerative colitis are described from time to time. During a five year period (1944–1949) four such instances were discussed in the Weekly Clinicopathological Exercises that appear in the *New England Journal of Medicine*.[7, 8, 9, 10]

The frequency with which cirrhosis occurs in patients with ulcerative colitis is unknown. Several reports, notably those of Ross and Swarts [11] and of Kimmelstiel, Large and Verner,[12] indicate that permanent liver damage in the form of cirrhosis is a relatively rare complication.

The data in this paper concern clinical observations relating to the association of chronic ulcerative colitis and cirrhosis. There are several reasons why the possible relationship of these two chronic disorders may go unrecognized. Both may run protracted courses. Patients with chronic disorders tend to go from one clinic or institution to another seeking relief. Single groups of physicians may not have the opportunity to witness the entire course of such diseases from the time of their onset until the final chapter is written. In the present series of cases, there are several instances in which the ulcerative colitis was in a quiescent phase; the patient no longer exhibited signs of colonic disease, and the clinical picture was dominated by the manifestations of cirrhosis. Unless one is particularly interested in the relationship of these two disorders, the natural tendency is to concentrate

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on the immediate problem at hand; the apparently unrelated events of the past medical history may excite little attention and pass unnoticed by the attending staff.

Material Studied

The case records of 287 patients studied at the University of Minnesota Hospitals during an 18 year period (1934–1952) have been reviewed. All of these patients had a diagnosis of idiopathic ulcerative colitis established by proctoscopic or roentgenologic means. Many had severe and protracted illnesses. The majority of these patients came to the University Hospital because of complaints directly referable to the ulcerative colitis, but some

Table I

Chronic Ulcerative Colitis and Cirrhosis
(Clinical Series)

Case No.	Sex	Ulcerative Colitis		Cirrhosis	Status	Age
		Onset at Age	Duration of Active Phase*	Diagnosis at Age		
1	M	12	5–6 years	19	Hepatosplenomegaly, deep jaundice	22
2	M	21	4–5 years	26	Recurrent hemorrhage from esophageal varices	29
3	M	21	8 years	34	Jaundice, hepatosplenomegaly	42
4	F	29	13 years	42 (at colectomy)	Died at age 44, extensive metastases from carcinoma of colon	—
5	F	29	32 years	61 (at colectomy)	Died at age 63, extensive metastases; known to have cancer of breast (1939) and cancer of colon (1950)	—

* Estimated from the medical history.

were first seen because of symptoms referable to hepatic disease. In the latter patients, the diagnosis of ulcerative colitis had been established at clinics elsewhere and that disease brought under control by various types of therapy.

Twelve cases in which the association of chronic idiopathic ulcerative colitis and cirrhosis was noted form the basis of this report. Five of these patients are described as clinical cases; the diagnosis of cirrhosis is based on evidences obtained by physical, laboratory and biopsy examinations. Two patients in this group are known to be dead; autopsy examinations were not performed. Seven patients have died as a result of cirrhosis, and necropsy data are available. Data relating to the 12 patients are summarized in tables 1 and 2.

Case Reports

Clinical Series:

Case 1. Male, age 21. The patient was studied at the University Hospitals in June and in October, 1952.

This boy had developed ulcerative colitis at the age of 12 years. The diagnosis was confirmed by examination at the Mayo Clinic three years after the diarrhea began. It was possible to control the symptoms by conservative medical means, and the patient enjoyed a fair degree of health until 1950, when he became jaundiced. The patient was then seen at still another clinic in 1950, where he was studied because of abdominal pain and jaundice. Abdominal exploration was carried out at that clinic and a biopsy of the liver and the pancreas was made. A cholecystogastrostomy was performed in September, 1950. The liver biopsy specimen was said to reveal chronic hepatitis. The operation produced no detectable decrease in the patient's jaundice. In June, 1952, the patient was referred to the University Hospital.

Table II

Chronic Ulcerative Colitis and Cirrhosis
(Autopsy Series)

Case No.	Sex	Ulcerative Colitis			Age at Death	Mode of Death	Pathology	
		Onset at Age	Clinical Severity				Colon	Liver
			Early	Late				
6	M	11	+++	+	14	Hepatic coma	Ulcerative colitis and ileitis, severe	2,200 gm., fatty (Laennec) cirrhosis
7	F	6	+++	Ileostomy, 8 months before death	14	Bleeding varices	Ulcerative colitis, healed	920 gm., postnecrotic cirrhosis
8	F	4	+++	Ileostomy, 3 years before death	19	Bleeding varices	Carcinoma of sigmoid colon; healed ulcerative colitis	1,150 gm., postnecrotic cirrhosis
9	F	11	+++	+	20	Sudden (see text)	Colitis polyposa	1,100 gm., postnecrotic cirrhosis
10	M	23	+++	Ileostomy, 8 months before death	31	Hepatic coma	Ulcerative colitis, healed	1,280 gm., postnecrotic cirrhosis
11	F	28	++	Asymptomatic	41	Bleeding varices	Ulcerative colitis, healed	1,700 gm., Laennec's cirrhosis
12	M	32	++	Asymptomatic	52	Bleeding varices	Ulcerative colitis, healed	1,475 gm., Laennec's cirrhosis

Physical examination at the time of this admission revealed a deeply jaundiced young man who appeared to be chronically ill. The liver was palpable as a very large, firm, nodular mass extending 10 cm. below the costal margin in the right midclavicular line. Considerable enlargement of the left lobe of the liver was also apparent; this

lobe was palpable 12 cm. below the xiphoid process. The spleen was greatly enlarged and was palpable 12 cm. below the left costal margin. The presence of free fluid in the peritoneal cavity was suspected; there was mild edema of the lower extremities. Clubbing of the fingers was prominent.

Laboratory studies revealed a total serum bilirubin level of 23 mg. per 100 ml.; the serum albumin was only to 1.6 gm. per 100 ml.; the serum globulin level was 4.4 gm. per 100 ml.

On proctoscopic examination, the colonic mucous membrane exhibited a granular appearance believed to indicate a quiescent phase of idiopathic ulcerative colitis. Needle biopsy of the liver was secured; the pathologist's diagnosis was chronic hepatitis. The presence of hepatosplenomegaly, icterus, ascites and clubbing of the fingers permitted a clinical diagnosis of cirrhosis. The patient was discharged and advised to follow a low salt, high protein diet.

The patient was seen again in October, 1952. The intensity of the jaundice and the physical findings remained unchanged, although the ascites and peripheral edema had disappeared.

Case 2. Male, age 29. The patient was admitted to the Medical Service at the University of Minnesota Hospitals in April and again in June, 1951.

This man had developed diarrhea at the age of 21 while in military service (1944). Jaundice was first observed in 1948 and has continued to the present time. In 1949 the patient was studied at the Mayo Clinic. A diagnosis of chronic ulcerative colitis was established by x-ray and proctoscopic examination. Jaundice was present; bromsulfalein dye retention was 40 per cent. A liver biopsy was interpreted as cirrhosis, grade III, by Dr. M. B. Dockerty.

In April, 1951, examination of the patient at the University Hospital revealed jaundice and ascites. Marked impairment of liver function was noted; hypoprothrombinemia, unresponsive to vitamin K, was noted; thrombocytopenia, so commonly seen in advanced cirrhosis, was likewise observed. Rectal bleeding was a prominent feature initially, but eventually this subsided. Sufficient improvement resulted from dietary and other measures to permit the patient to return to his home. His private physician, Dr. R. E. Brown, of Fort Dodge, Iowa, has kindly furnished data as to the current status of the patient. At present the ulcerative colitis is apparently inactive but signs of advanced liver disease persist. The patient has survived a severe episode of bleeding from a ruptured esophageal varix; this episode occurred late in 1952.*

Case 3. Male, age 44. The presence of cirrhosis was demonstrated in 1944; the disease has progressed very slowly and became incapacitating only recently.

This man developed ulcerative colitis in 1930 at the age of 21 years. The disease was controlled by conservative measures. In 1938 he experienced an exacerbation of his colonic disease. This was associated with the appearance of jaundice and hepatomegaly. In 1940 a diagnosis of cirrhosis was considered because of the presence of liver enlargement and abnormal liver function tests. During his seventh admission to the Medical Service of the University Hospital in 1944, hepatosplenomegaly was apparent. The serum bilirubin was elevated (3.9 mg. per 100 ml.); the cephalin-cholesterol flocculation test and the serum albumin level were normal. Needle biopsy of the liver disclosed the presence of cirrhosis. A barium enema study revealed evidence of chronic ulcerative colitis and, on x-ray examination, the presence of esophageal varices was suspected.

The patient was seen again in 1947 in the Out-Patient Clinic. The physical findings remained unchanged. In November, 1952, the patient reëntered the University Hospital complaining of severe left upper quadrant pain of 48 hours' duration. Examination revealed mild icterus and an enlarged, nontender liver. The area of

* Dr. Brown has informed the authors that the patient succumbed to a second episode of severe gastrointestinal bleeding in March, 1953.

splenic dullness was increased; there was tenderness on deep pressure over the spleen. The total serum bilirubin level was 5.2 mg. per 100 ml.; the cephalin-cholesterol flocculation test was negative. The presence of esophageal varices and of splenic enlargement, and the evidences of chronic ulcerative colitis were all demonstrated by roentgen examination. The patient refused to permit proctoscopic examination or needle biopsy of the liver; he left the hospital against advice. The presumptive diagnosis was splenic infarction in a patient with chronic ulcerative colitis and cirrhosis.

Case 4. Female, age 44. The patient died in 1948 of widespread metastases from a carcinoma of the colon.

A diagnosis of idiopathic ulcerative colitis was established at the Mayo Clinic in 1933, when the patient was 29 years of age. She was admitted to the Medical Service of the University Hospital in 1941 because of symptoms of active colitis. Anemia and skin pigmentation were noted. Conservative treatment was employed in the management of the colitis and the patient was able to leave the hospital.

A recurrence of severe diarrhea necessitated re-admission in 1944. Studies on the Medical Service revealed a palpable liver; liver function studies were within normal limits save for the cephalin-cholesterol flocculation test (2 plus). The patient was subsequently transferred to the Surgical Service, where an ileostomy was performed.

Later (in January, 1946) a colectomy was performed. Liver function tests at that time revealed a total serum bilirubin level of 3.9 mg. per 100 ml., a 2 plus cephalin-cholesterol flocculation test, and a 20 per cent retention of bromsulfalein dye. At operation a hobnailed liver was observed, and the diagnosis of cirrhosis was confirmed by examination of a liver biopsy. A small adenocarcinoma was found in the sigmoid portion of the resected colon; the adjacent lymph nodes contained cancer cells.

In June, 1948, the patient showed obvious signs of intraabdominal carcinomatosis; she died shortly thereafter. Autopsy examination was not permitted.

Case 5. Female, age 62. This patient died in 1952 of widespread pulmonary metastases. The primary neoplasm was probably a breast carcinoma, although she also had a cancer of the colon.

This patient developed ulcerative colitis in 1920 at the age of 29. In 1939 a radical mastectomy for carcinoma of the breast was performed. Her colonic disease remained intermittently active until January, 1950, when the patient was admitted to the Surgical Service of the University Hospital, where a colectomy and ileostomy were performed. Preoperatively, liver function tests revealed normal values for the bilirubin, bromsulfalein, cephalin-cholesterol flocculation and prothrombin tests. The serum albumin was 2.3 gm. and the globulin 4.7 gm. per 100 ml.; the total serum cholesterol was 126 mg. per 100 ml. At operation the liver appeared abnormal and the study of a biopsy disclosed cirrhosis. An adenocarcinoma of the colon was present in the resected specimen.

In April, 1950, the patient developed malaise, anorexia and jaundice. This was interpreted by her physician, Dr. F. G. Kolouch, of Schuyler, Nebraska, as an instance of homologous serum hepatitis; the patient had received several blood transfusions in January, 1950. After a stormy course in her local hospital the patient recovered and the jaundice disappeared.

In June, 1950, the patient returned to the University Hospital for evaluation and consideration of an abdominal exploratory operation (i.e., the so-called "second look" in a patient known to have had an abdominal carcinoma). Because of certain abnormalities (17 per cent bromsulfalein dye retention, 2 plus cephalin-cholesterol flocculation and a thymol turbidity value of 8 units), it was felt that recovery from the attack of viral hepatitis was probably incomplete. Operation was therefore postponed.

The patient returned in December, 1950, for the proposed operation. An enlarged left supraclavicular node was observed. Biopsy revealed carcinoma; this was

judged, on the basis of histology, to be from the breast cancer (1939) rather than from the cancer of the colon (1950). Liver function evaluation at this time revealed a negative cephalin-cholesterol flocculation test, a thymol turbidity of 7 units and 16 per cent bromsulfalein dye retention. The abdomen was explored. No evidence of abdominal metastases was observed. Biopsy of the liver revealed active inflammation and cirrhosis; presumably this represented viral hepatitis superimposed on a fairly stable or quiescent cirrhosis.

The patient received a course of deep x-ray therapy to the neck and axilla because of the late recurrence of the breast cancer. In June, 1952, signs of extensive pulmonary metastases were apparent and the patient died August 31, 1952. Autopsy was not performed.

Autopsy Series:

Case 6. Male, age 14. This boy died in May, 1939, in hepatic coma.

Diarrhea, at times bloody, occurred when the patient was 11 years of age. Later the boy was examined at the Mayo Clinic, where a diagnosis of ulcerative colitis was established. At that time the liver was observed to be enlarged and tender; dye retention, grade III, was reported. The patient was first seen on the Pediatric Service of the University of Minnesota Hospitals in 1938. At that time the diarrhea was moderately severe; the diagnosis of ulcerative colitis was confirmed. In January, 1939, the patient was again admitted for treatment of ethmoiditis and pneumonia. His third and final admission to the Pediatric Service was in March, 1939. The chief complaint at that time related to abdominal distention; diarrhea was less severe than formerly. Examination revealed a pale, emaciated boy with marked ascites. Palpation following removal of the abdominal fluid revealed an enlarged and tender liver. Various therapeutic measures were employed but the patient's condition gradually deteriorated. He died in a state of hepatic coma on the twenty-fourth hospital day.

At autopsy the pertinent findings were limited to the abdominal cavity. The liver weighed 2,200 gm. and had a finely granular surface. It was a pale yellowish brown in color. Cross sections through the liver indicated that these changes were uniform. The extrahepatic biliary duct system was normal. The spleen weighed 325 gm. The distal 12 inches of the ileum revealed marked thickening and mucosal discoloration. These pathologic changes continued on into the colon. The mucosa of the large bowel was extensively involved. The mucosa throughout the entire colon exhibited minute ulcerations.

Microscopic examination of the liver revealed a markedly fatty cirrhosis. Microscopic examination of the colon and ileum confirmed the diagnosis of chronic ulcerative colitis and ileitis.

Case 7. Female, age 14. This girl died in hepatic coma in October, 1947.

The child had first developed diarrhea at the age of six; the number of stools varied from three to 15 per day and were frequently bloody. The diarrhea continued with periods of exacerbation and remission. In November, 1946, an episode of nausea and vomiting was followed by the appearance of jaundice. The bloody diarrhea became increasingly severe. One week after the onset of jaundice the patient was seen at the Willmar Clinic, Willmar, Minnesota. Examination revealed an undernourished and poorly developed child. Pallor, jaundice, hepatosplenomegaly and spider nevi were observed. Laboratory studies indicated marked impairment of liver function. X-ray examination of the colon revealed the characteristic changes of ulcerative colitis. Treatment at this time included a high protein diet, fortified with vitamin concentrates, antibiotics and the administration of a crude liver extract. A remission was induced which lasted two months.

The child was admitted to the Pediatric Service of the University of Minnesota Hospital in February, 1947. The physical findings were similar to those noted in November, 1946, viz., jaundice and enlargement of the liver and spleen. Prominent

veins were noted over the abdominal surface. A proctoscopic examination revealed lesions characteristic of advanced ulcerative colitis. Marked impairment of liver function was again demonstrated by laboratory studies. A clinical diagnosis of chronic ulcerative colitis and cirrhosis was made.

The treatment employed at this time was aimed at improving the nutritional status. Multiple transfusions of blood and plasma were given. The bloody diarrhea continued during the patient's stay in the hospital; after three weeks an ileostomy was performed. A needle biopsy of the liver secured at this time revealed signs of an active hepatitis and evidences of cirrhosis. Immediately following the operation there was an increase in the severity of the patient's jaundice; the total serum bilirubin

FIG. 1. Photomicrograph × 30; liver at autopsy, case 7. Areas of extensive scar formation, new bile duct formation and the presence of regenerative nodules are shown. (Azocarmine B stain.)

level rose from 4.8 to a maximum of 43.3 mg. per 100 ml. Despite the apparent increase in the severity of the liver functional impairment, the patient's condition improved somewhat following establishment of the ileostomy. There was a gradual gain in weight, and the intensity of the jaundice slowly diminished. By May, 1947, the serum bilirubin had declined by 7.1 mg. per 100 ml., and the patient was able to leave the hospital, to be followed in the Out-Patient Clinic.

In August, 1947, it was necessary to re-admit the patient to the Pediatric Service because of increasing jaundice. Examination revealed the presence of ascites; there were prominent venous collateral channels over the abdomen. Spider nevi were numerous. A fetor hepaticus was detected. Serial laboratory studies revealed further

deterioration in hepatic function. An esophagram at this time revealed extensive esophageal varices. The child lived until October, 1947; repeated hemorrhages from ruptured esophageal varices occurred, hepatic coma developed, and the child died.

At autopsy the peritoneal cavity contained approximately 3 L. of a yellow fluid. The small bowel and the stomach were markedly distended with old blood. The liver was dark green in color and coarsely nodular. On cut sections the liver parenchyma appeared to have been largely replaced by fibrous tissue. The changes were characteristic of an advanced postnecrotic cirrhosis. The liver weighed 920 gm.; the spleen weighed 420 gm. The extrahepatic biliary duct system was normal. Definite varices were demonstrated in the lower part of the esophagus. The terminal ileum appeared to be normal and the ileostomy appeared to be in a satisfactory condition. The colon was markedly contracted; there was no gross evidence of ulceration. Microscopic examination of the liver confirmed the impression of postnecrotic cirrhosis (figure 1). Microscopic study of sections taken from the colon revealed some infiltration of mononuclear cells into the muscularis mucosae and into the submucosa. The pathologic diagnoses were: (1) ulcerative colitis; (2) postnecrotic cirrhosis; (3) esophageal varices, with recent hemorrhage.

Case 8. Female, age 19. This girl died at the University Hospital in August, 1945. Cancer of the colon with widespread metastases existed; the immediate cause of death was hemorrhage from esophageal varices secondary to cirrhosis.

The patient was first admitted to the Medical Service in July, 1941, because of a recent hematemesis. The initial examination revealed a pale, emaciated and markedly underdeveloped 16 year old girl; hepatosplenomegaly and ascites were apparent. The superficial veins over the abdomen were prominent. The clinical history revealed that the patient had first exhibited diarrhea at the age of four years. The diarrhea persisted and was marked by passage of blood and mucus at intervals. The girl was chronically ill throughout her childhood. Jaundice was first noted at the age of 10 years.

The presence of chronic ulcerative colitis was established by x-ray and proctoscopic examination. A diagnosis of cirrhosis was entertained and, although esophageal varices were not demonstrated, their presence was suspected as a cause of the recent hematemesis. As a result of transfusions, dietary measures and sulfonamide therapy, the patient improved and was discharged after two months.

The patient's improvement was short-lived; she was re-admitted in November, 1941, with an exacerbation of the bloody diarrhea. Physical findings were similar to those noted on the initial admission, although the ascites had decreased. Jaundice (total serum bilirubin, 2.9 mg./100 ml.) and liver functional impairment were again demonstrated. It proved impossible to control the diarrhea by conservative means. In December, 1941, the patient was transferred to the Surgical Service, where an ileostomy was performed. Following this operation the patient exhibited a most remarkable improvement. The rectal discharge was reduced to a minimum and she gradually lost her ascites. Within one year her body weight more than doubled.

The patient was seen at intervals at the Out-Patient Clinic. In April, 1943, the serum bilirubin was 1.5 mg. per 100 c.c. and the bromsulfalein dye retention had dropped to 3 per cent. Satisfactory progress continued until June, 1945, when crampy abdominal pain with radiation to the back occurred. This was associated with rectal bleeding. A barium enema revealed a constricted area in the descending colon, interpreted as evidence of active colitis. Colectomy was advised and the patient was admitted to the Surgical Service.

Investigation at this time revealed anemia, leukopenia and evidence of liver functional impairment. Shortly after admission a thrombophlebitis involving the right femoral vein developed. The colectomy was postponed and treatment with anticoagu-

lants and antibiotics was instituted. During this period the presence of enlarged supraclavicular lymph nodes on the left side was detected. A lymph node biopsy revealed metastases from a gelatinous carcinoma. The proposed colectomy was deferred. The patient's condition rapidly deteriorated. Terminally the patient had several hematemeses.

Autopsy examination revealed a poorly developed white girl; there was generalized icterus present. The peritoneal cavity contained 1,500 c.c. of a blood-tinged, slightly clouded fluid. The liver weighed 1,150 gm.; it had a marked hobnail appearance externally, and cut with difficulty because of the gross fibrosis present. The spleen weighed 630 gm.; the splenic vein contained a thrombus. Examination of the

FIG. 2. Photomicrograph × 30; liver at autopsy, case 8. The presence of irregular scarring and nodular regeneration is shown. In other areas, the wider bands of scarring were seen. (Azocarmine B stain.)

esophagus revealed many dilated veins. The mesentery of the small intestine was thickened and indurated by carcinomatous infiltration. No abnormalities of the small bowel mucosa were noted; the ileostomy site appeared to be in a satisfactory condition. A large tumor mass measuring 15 cm. in length was noted in the descending colon. The remainder of the mucosa of the large bowel was extremely smooth and atrophic. There were numerous metastatic tumor nodules in the lungs.

Microscopic examination of the colonic tumor demonstrated a gelatinous carcinoma. There were miliary metastases in the lungs. Sections of the liver revealed the characteristic changes of a postnecrotic cirrhosis (figure 2).

Case 9. Female, age 20. This patient died in September, 1951; far advanced cirrhosis was present.

The patient was 11 years of age when she first developed severe diarrhea. A migratory polyarthritis was a prominent early feature of her illness. The diagnosis of ulcerative colitis was established at the Mayo Clinic in 1942. A medical regimen was employed to control the diarrhea. By 1945 the proctoscopic appearance of the colon suggested a healing process. A prominent feature of this girl's illness from 1945 to 1948 was the occurrence of deep necrotic ulcers of the left leg. These proved very resistant to treatment and eventually required skin grafting.

The first clinical evidence of hepatic disease was the appearance of bilirubinuria in January, 1951. In May, 1951, definite jaundice was apparent and ascites developed. The patient was admitted to the Medical Service of the University of Minne-

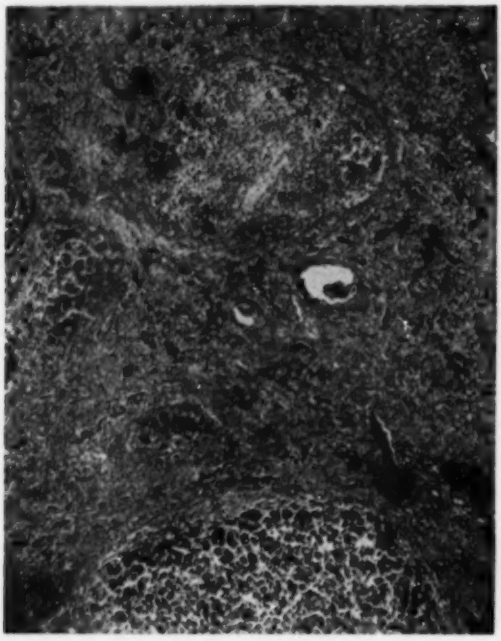

FIG. 3. Photomicrograph × 30; liver at autopsy, case 10. Postnecrotic cirrhosis with scar formation. Sections from other areas in this liver resembled that of figure 2. (Hematoxylin and eosin stain.)

sota Hospitals in September, 1951. She was anemic, icteric and markedly emaciated. The hemoglobin level was 4.5 gm. and the total serum bilirubin, 6.7 mg. per 100 ml. The abdomen was markedly distended with free fluid; the spleen was palpable; enlargement of the liver could not be demonstrated. Liver functional impairment was marked, as judged by the results of customary tests. The serum cholesterol value was 60 mg. per 100 ml.; the serum albumin level was only 0.8 gm. per 100 ml. Febrile reactions occurred following attempted blood transfusions; the patient's condition deteriorated rapidly. She died suddenly while receiving an infusion of plasma.

At autopsy examination the body was that of a white female whose general development indicated apparent growth failure. There was extreme emaciation; mode-

rate icterus was present. The abdomen was markedly distended; there were many dilated veins over the anterior chest wall. A large ulcerated area was noted over the lower part of the left leg. The peritoneal cavity contained 9 L. of a clear, straw-colored fluid. The liver weighed 1,000 gm. and was definitely shrunken in all diameters. The surface was coarsely nodular and, on cut section, the characteristic changes of a postnecrotic cirrhosis were apparent (figure 4). The spleen weighed 850 gm. Esophageal varices were demonstrated. The small bowel appeared normal. Examination of the colon revealed extensive disease in the form of colitis polyposa. The descending colon showed extreme ulceration, polyposis and hypertrophy of the mucous membranes.

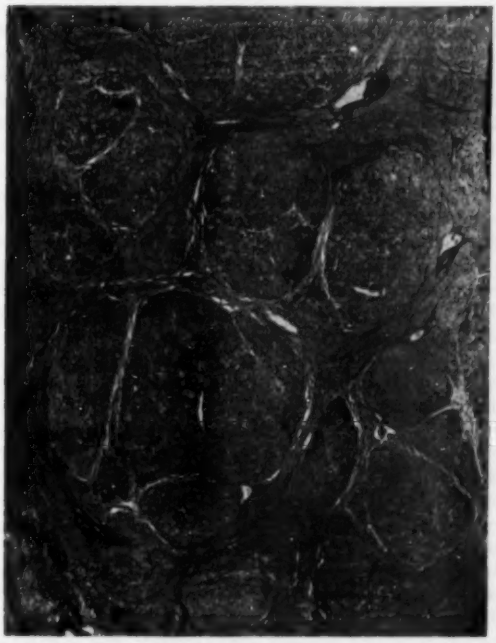

FIG. 4. Photomicrograph × 10; liver at autopsy, case 9. Postnecrotic cirrhosis; the regenerative nodules and scarring are shown; at the lower magnification employed, the bands separating the nodules appear thin in comparison with the other figures. (Azocarmine B stain.)

Microscopic examination confirmed the gross diagnoses of (1) chronic ulcerative colitis and colitis polyposa, and (2) cirrhosis of the postnecrotic type.

Case 10. Male, age 31. The patient died in hepatic coma in December, 1948.

He was first seen at the Mayo Clinic in 1941, where a diagnosis of idiopathic ulcerative colitis was established. The onset of this disease was acute; the initial illness was marked by fever and arthritis and the frequent passage of bloody stools. Supportive treatment and blood transfusions succeeded in arresting the disease. The colonic disorder remained quiescent and the patient enjoyed fair health until 1947, when jaundice appeared.

The patient was first seen at the University Hospital in April, 1948. A clinical diagnosis of cirrhosis was made on the basis of hepatomegaly, jaundice, ascites and

marked impairment of liver function. Proctoscopic examination disclosed a "healing" ulcerative colitis. After careful deliberation an ileostomy and an eventual colectomy were proposed. Although the patient was not incapacitated by his colitis, it was hoped that the apparently relentless progress of the liver disease might be arrested by eventual extirpation of the diseased colon. In May, 1948, an ileostomy was performed under local anesthesia. The patient recovered from the operation uneventfully but failed to show any improvement in liver function.

In November, 1948, he was re-admitted because of continued jaundice and the recent development of mental confusion. The final month of life was marked by intermittent episodes of unconsciousness; terminally, the characteristic features of hepatic coma were apparent.

Autopsy examination revealed that the body was well developed and well nourished. There was marked icterus. The ileostomy site appeared to be in a satisfactory condition. The peritoneal cavity contained 350 c.c. of a cloudy yellow fluid. The liver weighed 1,280 gm. The external surface was rather pale reddish brown in color and was studded with innumerable small nodules. On cut surface the liver revealed an increased content of fibrous connective tissue. The extrahepatic biliary duct system was normal. The spleen weighed 325 gm. The esophagus, stomach and small bowel presented no abnormalities. The entire colon was narrow and the wall was thicker than normal. Microscopic examination of the liver revealed the characteristic changes of a postnecrotic cirrhosis (figure 3); the parenchyma was divided into coarse lobules by thick strands of dense fibrous connective tissue. The parenchyma cells that remained were bile stained and showed various degrees of degeneration. There was marked evidence of attempted regeneration of liver tissue in the form of varying sized nodules. Sections of the colon showed little or no pathologic change save for a slight fibrosis of the muscularis mucosae.

The pathologic diagnoses were: (1) chronic ulcerative colitis, healed (clinical); (2) ileostomy, old; (3) cirrhosis of liver, severe, active, postnecrotic type.

Case 11. Female, age 41. This patient was studied at the University of Minnesota Hospitals in April, 1950. Death occurred in August, 1951, following a massive gastrointestinal hemorrhage, the result of a ruptured esophageal varix. During her final illness the patient was under the care of Dr. G. C. Blome, of Ottumwa, Iowa. The authors are grateful to him and to Dr. C. R. Phelps, pathologist at the Physician's Clinical Laboratories, Ottumwa, Iowa, for permission to report this case.

The patient experienced her first manifestation of ulcerative colitis at the age of 28. This diagnosis was confirmed two years later when, in 1940, she was examined at the Mayo Clinic. Evidence of early liver damage was reported at that time. Under conservative management the diarrhea was controlled. In 1943 the patient became pregnant. No immediate aggravation of the colitis occurred and she delivered a normal infant at full term.

During the ensuing six years the patient experienced intermittent attacks of diarrhea. Jaundice developed insidiously. In 1949 the patient was again examined at the Mayo Clinic, where a diagnosis of cirrhosis was made and a guarded prognosis offered. In 1950 the patient was referred to one of the authors (C. D.) for consideration of ileostomy and colectomy. Study at this time revealed clear evidence of advanced cirrhosis; esophageal varices were demonstrable by x-ray examination. In view of the quiescent nature of the colitis and the presence of cirrhosis, the patient was advised that removal of the colon was not indicated.

She remained jaundiced throughout the remainder of her life. She died August 31, 1951. The immediate cause of death was hemorrhage from an esophageal varix. Autopsy examination, performed by Dr. Phelps, revealed a rent in one of the large esophageal veins. The liver weighed 1,700 gm. and exhibited nodular areas of re-

generation throughout. The spleen was markedly enlarged. The large intestine showed no evidence of ulceration; the mucosa was very flat and atrophic. There was irregular thickening of the wall of the colon. Dr. Phelps' diagnosis was: (1) arrested ulcerative colitis; (2) cirrhosis of the liver, portal type; (3) splenomegaly, and (4) esophageal varicosities, with rupture of one vessel.

Case 12. Male, age 52. This patient died at the University Hospital in 1942. Death followed hemorrhage from esophageal varices.

The patient first experienced troublesome diarrhea in 1921, when he was 32 years of age. A diagnosis of ulcerative colitis was established at the Mayo Clinic. The disease was controlled by medical measures and never became incapacitating. In 1931 the patient experienced biliary colic followed by jaundice. A cholecystectomy afforded him relief and he experienced no further attacks of jaundice. He was able to control his bouts of diarrhea with such medications as paregoric.

In July, 1941, at the age of 51, the patient noted the onset of ascites. Abdominal paracenteses were necessary. He entered the University of Minnesota Hospital in October, 1941, and remained there until his death on March 1, 1942. Examination at the time of admission revealed ascites to be present. Following removal of the fluid the liver was palpable. Splenomegaly was not detected. A few spider nevi were visible; palmar erythema was prominent.

Laboratory studies revealed moderate impairment of hepatic function, although visible icterus was absent (total serum bilirubin, 1.5 mg. per 100 ml.). The proctoscopic examination disclosed changes consistent with a quiescent phase of ulcerative colitis. X-ray examination by means of a barium enema revealed evidence of a chronic ulcerative colitis involving the entire colon.

The control of the recurrent ascites proved very difficult for, in 1941, the need for sodium restriction was not appreciated. The patient developed an ischiorectal abscess during his first month in the hospital; surgical drainage was required. His clinical condition gradually deteriorated. Coma followed the occurrence of severe hemorrhage from the stomach and esophagus.

At autopsy the body appeared to be well developed but poorly nourished. The right pleural cavity contained 1,500 c.c. and the left pleural cavity 400 c.c. of a clear straw colored fluid. Examination of the peritoneal cavity revealed numerous fibrous adhesions, most marked in the lower abdomen. The liver weighed 1,475 gm.; its surface was finely hobnailed and coarsely divided into indefinite lobules. On section the liver cut with increased resistance. The cut surface was somewhat rough and finely lobulated. The gall-bladder area was surrounded by fibrous adhesions. There was no obstruction of the common bile duct. The spleen weighed 575 gm.; it was smooth and pale. The gastrointestinal tract revealed numerous large varices confined to the lower third of the esophagus. The stomach and small intestines were filled with old blood. The colonic mucosa was diffusely thickened; this was most marked in the region of the descending colon. There was no evidence of fresh ulceration. Microscopic examination revealed a cirrhosis classified as the portal (Laennec) type. The pathologic diagnosis was: (1) cirrhosis, portal type; (2) ulcerative colitis, healed stage; (3) esophageal varices, with recent hemorrhage.

Discussion

The observed association of cirrhosis in 12 instances in a series of 287 patients known to have ulcerative colitis would appear to be an unusually high incidence.

As indicated, this survey extends over an 18 year period. Furthermore, this is admittedly a selected group of cases of ulcerative colitis. It includes

many patients with severe and long standing disease; many were referred to the University of Minnesota Hospitals not only because of their colonic disease but also because of complications relating to that disorder. The difficulties encountered in attempting to determine the exact incidence of this association are readily apparent; they include the problem of following patients over long periods of time, and the problem of establishing the diagnosis of the two disorders under consideration.

The cases described in this report have been limited to those believed to be undoubted instances of the development of cirrhosis in a patient with ulcerative colitis. Six additional cases in the total series of 287 patients with ulcerative colitis might be briefly mentioned. They were patients considered, on the basis of clinical examination, to be examples of this association. At necropsy, two of the patients had focal areas of fibrosis in the liver; this was not sufficient pathologic evidence to warrant a diagnosis of cirrhosis. Two patients with past medical histories very suggestive of ulcerative colitis exhibited postnecrotic cirrhosis at autopsy; pathologic examination of the colon at that time did not disclose the presence of characteristic changes. Since the presence of idiopathic ulcerative colitis had not been established with certainty, these two individuals were not included in this report. A fifth patient, a child, proved at necropsy to have acute hepatic necrosis rather than cirrhosis. The sixth patient in this particular group is living; the diagnosis of cirrhosis seems reasonably certain, but a liver biopsy has not been secured.

The type of cirrhosis encountered in the patients in this study does not appear to be uniform, to judge from the pathologic descriptions. The difficulties encountered in attempts to classify cirrhosis on the basis of morphology are well recognized; the problem is summarized in a report that appeared in 1947.[13] Any attempt that might be made to discuss the type of cirrhosis present in the five patients designated "clinical series" must of necessity be limited. A liver biopsy is usually inadequate to permit definition as to the type of cirrhosis, except in a few well recognized conditions such as hemochromatosis, fatty infiltration and similar disorders. None of the biopsy specimens from these five patients exhibited fatty infiltration. To deny that such patients may not have had a previous fatty infiltration of the liver is not possible; none of the remnants of earlier fatty infiltration described by Hartroft [14] was detected in these specimens.

The clinical course of the cirrhotic process in cases 1 and 2 appears to be one of fairly rapid progression. The hepatic disease has been present for three years and the patients are both quite incapacitated. The progress of the cirrhosis in case 3 appears to have been more gradual, but recent events suggest that deterioration of hepatic function is continuing. The natural course of the hepatic disease in cases 4 and 5 could not be ascertained, since the patients' lives were terminated by cancer.

The seven cases (table 2) in which autopsy data are available do permit

some discussion of the type of cirrhosis that existed. In only one instance (case 6), a boy of 14, was fatty cirrhosis observed. The liver was large, fatty infiltration was uniform and the fibrosis was diffuse in nature. Two instances of Laennec's, or portal, cirrhosis (cases 11 and 12) were observed. The difficulty in deciding what etiologic factor or factors were responsible is obvious. Alcoholism was denied by both patients. Although the difficulties in interpreting medical histories in this connection are appreciated, the statements of these patients appeared to be reliable. In both patients the cirrhotic process appeared to progress, albeit slowly, in spite of the fact that the colitis was in a quiescent phase and presumably the dietary intake was fairly adequate.

Four of the patients described in table 2 (cases 7, 8, 9 and 10) exhibited a postnecrotic cirrhosis. The hepatic lesion has been variously termed toxic cirrhosis, healed acute yellow atrophy or coarsely nodular cirrhosis. The etiology is obscure; it seems unlikely that it is the result of a nutritional deficiency. Judging from clinical experience in other patients with postnecrotic cirrhosis, the disease appears to progress relentlessly despite an adequate food intake. Attempts to reproduce this disorder in experimental animals by feeding deficient diets that are necrogenic have not met with success.[15] It would appear from the results in case 8, however, that striking benefit did occur after the patient was subjected to ileostomy. Despite the fact that this was performed when the patient had obvious evidence of advanced hepatic disease (ascites was present), the clinical improvement that followed was remarkable. It is most regrettable that a total colectomy was not performed earlier and the development of carcinoma prevented. In 1941, when the ileostomy was performed, the surgical treatment of ulcerative colitis was less well defined than it is now. No such benefit occurred in cases 7 and 10; ileostomy in these patients appeared to exert little influence on the course of the hepatic disease. Case 7, a child of 14, had active colitis at the time; the colonic disease was quiescent in the other patient, case 10, a 31 year old man. In this latter instance the ileostomy was performed on the bare chance that it might possibly benefit the patient and halt the progress of his postnecrotic cirrhosis.

The possibility that the patients exhibiting postnecrotic cirrhosis might represent instances of chronic viral hepatitis must be considered. Certainly, individuals with ulcerative colitis may well have opportunities to become victims of this virus disease. If the agent is present in the feces, as it appears to be in infectious or epidemic hepatitis (virus type IH or type A), there would appear to be an excellent opportunity for the virus to enter the portal circulation through the ulcerated colonic mucosa. If the agent does not reach the patient by that route, there are many opportunities for patients with ulcerative colitis to develop homologous serum hepatitis (virus SH or type B). Most patients with this colonic disease receive injections, trans-

fusions or infusions at some time or other in the course of treatment. The possible rôle of the viral hepatitis in the development of cirrhosis cannot be clarified at present. That relationship probably will remain obscure until a suitable biologic test for the recognition of the agents is discovered. It is of some interest that one patient in this series (case 5) appeared to develop homologous serum hepatitis three months after the colectomy was performed. The diagnosis of cirrhosis was established at the time of colectomy. It would appear, therefore, that the viral hepatitis was superimposed on an already existing cirrhotic process and that the patient recovered despite this handicap. A liver biopsy taken nine months later revealed cirrhosis and evidence of recent inflammation, the latter presumably from the attack of hepatitis. As noted, this patient died two years later as the result of late metastases, probably from a breast carcinoma. There was no opportunity to examine the liver after death.

The part that viral hepatitis may play in the production of liver damage and cirrhosis in ulcerative colitis has been well reviewed by Kleckner and his associates.[9]

The possible relationship of viral hepatitis to colonic bacteria is one of considerable importance and interest. This subject has been recently reviewed by Stokes.[16] The possible implications in any consideration of the development of hepatic disease in ulcerative colitis are apparent.

The question can well be raised, What, if any, is the relationship of ulcerative colitis and cirrhosis? No satisfactory answer can be furnished at present. On the basis of clinical observations, there would appear to be a relationship, at least in the sense that the late development of cirrhosis must be regarded as a complication of this type of colonic disorder. In 1938, Comfort, Bargen and Morlock [1] emphasized the features of the long standing nature of the disease, the low-grade activity of colitis, the minimal anatomic deformity of the colon and the presence of chronic hepatic disease. This occurred in three of the four cases described in which chronic ulcerative colitis was associated with liver disease. This sequence of events is reflected in the cases described in the present report.

As noted, the development of cirrhosis is often a slow process. This appears to be particularly true in adult patients. In younger individuals the disease tends to develop and progress somewhat more rapidly. If one attempts to correlate the development of hepatic disease with some antecedent disorder such as ulcerative colitis, the entire course of the two disorders must be considered.

Summary and Conclusions

1. The clinical course of 12 patients exhibiting the association of chronic ulcerative colitis and cirrhosis has been reviewed. The cases were selected from the records of 287 patients with ulcerative colitis seen at the University of Minnesota Hospitals during an 18 year period (1934–1952).

2. In five patients (three males and two females), the diagnosis of cirrhosis was established on the basis of physical, laboratory and biopsy findings. The three male patients are living; the colitis is inactive but the manifestations of cirrhosis, jaundice or recurrent episodes of bleeding from varices are prominent features of the clinical picture at present. The diagnosis of cirrhosis was established in the two female patients at the time colectomy and ileostomy for long standing chronic ulcerative colitis were performed. Both patients had carcinoma of the colon; both died of metastatic cancer two years later. Necropsies were not performed.

3. In seven patients (three males and four females), autopsy data were available. The terminal clinical manifestations in these patients were those of advanced cirrhosis, i.e., bleeding from varices and hepatic coma. One patient, a 19 year old female, developed a carcinoma of the sigmoid colon three years after ileostomy had been instituted. Widespread metastases as well as a postnecrotic form of cirrhosis were present at postmortem examination. The pathologic diagnoses in the remaining six patients were: ulcerative colitis (severe) and fatty cirrhosis, one case; colitis polyposa and postnecrotic cirrhosis, one case; ulcerative colitis (healed) and postnecrotic cirrhosis, two cases; ulcerative colitis (healed) and Laennec's cirrhosis, two cases.

4. The relationship of ulcerative colitis to the development of cirrhosis is obscure. Clinical observations suggest that the frequency of occurrence may be greater than is generally appreciated. Figures based upon autopsy findings in patients dying of ulcerative colitis per se, especially if the disease was of short duration, are not likely to indicate the true incidence of the occurrence of cirrhosis.

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DISEASE OF THE LIVER ASSOCIATED WITH ULCERATIVE COLITIS *

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For many years we have been aware that disturbance of liver function and secondary disease of the liver occur among patients with long-standing ulcerative colitis. As early as 1930 Giffin and I [1] reported cases of a condition which we called "infectious hepatosplenomegaly," and which, in many ways, resembled Banti's disease, although it usually occurred in young people. In most of the cases which we reported at that time the ultimate cause of death was cirrhosis of the liver and hepatic failure.

Some years later, Comfort, Morlock and I [2] reviewed four cases in which disease of the liver, with jaundice, had developed late in the course of ulcerative colitis. The jaundice, while intermittent at first, eventually was persistent and continuous and again in these cases, as in those mentioned earlier, death was caused by disease of the liver rather than by the ulcerative colitis itself.

In 1951 and 1952 my associates and I performed a series of biopsies on the livers of patients who had ulcerative colitis in various stages of development. The results of these experiences were reported a year ago [3] before the meeting of the American Gastroenterological Association. It will be recalled that the patients in this group were selected. Serious complications did not occur as a result of the biopsies, but in two cases a phenomenon, which might be considered as so-called pleural shock, developed immediately after transpleural biopsy. The patients, however, recovered promptly.

Twenty-six patients were selected because of clinical or laboratory evidence suggestive of hepatic disease. Six other patients who had undergone biopsy but who were without signs or symptoms of hepatic dysfunction served as controls. In this group of six controls, two patients were demonstrated to have a normal histologic picture, two had infiltration with fat and two had pericholangitis.

Histologically, five of the 26 patients were found to have normal livers; three had 8 per cent or more retention of sulfobromophthalein dye at the end of one hour. Two of the patients had fever, which is known to increase the percentage of dye retained, and one patient with 40 per cent retention of dye had severe anemia from loss of blood, which may have affected the sulfobromophthalein test because of a diminished flow of hepatic blood.

The livers of nine patients were infiltrated with fat, but in none of these could the specific lesion have been suspected from the clinical or laboratory survey. Seven of these nine patients had abnormal retention of sulfobromo-

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phthalein (more than 5 per cent). Five of these seven patients had associated fever, which could have affected the test; two patients did not have fever, and it is likely that the infiltration of the liver with fat was responsible for the abnormal value. The result of the thymol turbidity test was negative in all nine cases. The result of the cephalin-cholesterol test of one patient was 3 plus. Four of the nine patients with infiltration of fat had received aureomycin or terramycin. Since there have been recent reports of infiltration of the liver with fat in association with the use of aureomycin, it is possible that this drug may have been a factor in these cases. However, the livers of eight other patients in this series who had received aureomycin or terramycin were without evidence of infiltration with fat; therefore, conclusions could not be drawn about its effect in this series. Only one patient whose liver was infiltrated with fat had an abnormal value for serum bilirubin; in this instance the value was 1.1 mg. per 100 c.c., and the van den Bergh reaction was direct. It is of interest that in eight cases only minor histologic changes were associated with the infiltration with fat, and in none was cirrhosis an associated condition. It has been mentioned that diffuse fatty cirrhosis is often seen at necropsy in cases of chronic ulcerative colitis. However, according to a study by Jones, Baggenstoss and myself,[4] the transformation of a fatty liver into a cirrhotic liver occurs rather infrequently; in necropsy studies of 91 cases of chronic ulcerative colitis, we found fatty cirrhosis in only two instances, although infiltration of the liver with fat was present in 47.

Infiltration of the liver with fat both in human beings and in animals has been a topic of much discussion and investigation. It would seem that in patients having chronic ulcerative colitis many conditions and factors, such as malnutrition, lack of lipotropic agents, anemia and the toxic effects of undetermined bacterial or chemical products, might be present which would contribute to the production of a fatty liver.

Of unusual interest in this study were the five cases in which the histologic findings were pericholangitis with stasis of bile, which was present in three, and diffuse hepatitis, also present in three. In all cases chronic ulcerative colitis was existent prior to the development of icterus. The duration of jaundice in these five cases varied from two months to three years. None of these patients had received transfusions of blood or plasma prior to the onset of jaundice. The question arises as to the possibility that these were cases of infectious hepatitis. Weir [5] has commented that in most cases jaundice associated with chronic ulcerative colitis becomes chronic and lasts for months or years, along with the development of other signs or symptoms of hepatic failure. In our experience this protracted course of jaundice seems to be the rule in cases of chronic ulcerative colitis, a fact which might be used as an argument against viral hepatitis, in which spontaneous clearing of the jaundice is the rule rather than the exception.

The clinical picture in these five cases was similar to that in cases of

chronic hepatitis with jaundice as described by Weir and Snell,[6] and cholangiolitic hepatitis described by Watson and Hoffbauer.[7] The value for alkaline phosphatase of four patients with this clinical picture was elevated, but that for serum cholesterol was essentially normal in all cases. Two of the three patients who were found by biopsy to have pericholangitis with stasis of bile had a reversed albumin-globulin ratio and an abnormal reaction to the zinc sulfate turbidity test. This probably is indicative of a transition toward primary biliary (cholangiolitic) cirrhosis.

In three instances my colleagues and I considered a diagnosis of postnecrotic cirrhosis. However, it has been the experience of two of us (Stauffer and Dockerty) that a diagnosis of postnecrotic cirrhosis based on needle biopsy is highly questionable. It should be mentioned that not all pathologists are in agreement as to the microscopic criteria for the diagnosis of this disease. Two patients with cirrhosis had been jaundiced for five months and a viral etiology could be speculated.

In discussion of postnecrotic cirrhosis associated with chronic ulcerative colitis, attention has been called to the work of Himsworth and Glynn,[8] who produced postnecrotic lesions in rats by using a diet deficient in protein. Alteration of this diet produced an entirely different hepatic lesion, characterized by infiltration with fat and subsequent transition into what they called "portal cirrhosis."

Although pathologists are of the opinion that most cases of postnecrotic cirrhosis in the human being are the result of viral hepatitis, the occasional discovery of this lesion in association with chronic ulcerative colitis when nutritional deficiencies and bacterial infections are so evident makes this combination worthy of comment.

In the cases in which histologic findings of pericholangitis with stasis of bile, diffuse hepatitis and cirrhosis were present, the majority of patients had had a reversal of the albumin-globulin ratio, and positive results to tests for thymol turbidity, zinc sulfate turbidity and cephalin-cholesterol flocculation. Definite conclusions cannot be drawn concerning the possibility that the disease in these cases might have been viral hepatitis.

It is interesting to note that, of eight patients seen at the Mayo Clinic and later at the University of Minnesota Hospitals, the youngest was 12 years of age when seen at the clinic and the oldest was 34 years of age. Most of these patients were seen only once and for diagnosis alone. Five of them had extensive and advanced disease with involvement of the entire colon. In two of them hepatitis had developed unrelated to colitis; in fact, hepatitis had developed in one patient after he had entered the Navy, his colitis having been quiescent for some time. In one case jaundice developed at a time when the patient also had pyoderma gangrenosum. In three cases the patients' colitis had been quiescent for a considerable time before symptoms of hepatitis were recognized. Evidence of cirrhosis was present in only one patient. The question of the relation between ulcerative colitis

and hepatitis or, later, between ulcerative colitis and cirrhosis comes up frequently. In some of the patients who have ulcerative colitis and hepatitis, there is little doubt that the hepatitis occurs as a result of the colitis; in others, some doubt remains. It is rather amazing that this complication does not occur more frequently among patients with severe ulcerative colitis, but, in any event, it is of such serious moment that further careful study of the problem is indicated.

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SOME OBSERVATIONS ON THE RELATIONSHIP BETWEEN WEIGHT CHANGES FOLLOWING SODIUM RESTRICTION AND THOSE ASSOCIATED WITH THE MENSTRUAL CYCLE IN NORMAL YOUNG WOMEN*

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GENERALIZED edema has been observed to occur in association with the onset of menstruation in a significant proportion of normal women.[1-4] Although this is, perhaps, the only type of generalized edema which is physiologic in origin, little is known about the reasons for its occurrence.[5, 6] Sweeney found that while 30 per cent of 42 healthy nurses gained three or more pounds of body weight in the premenstrual or menstrual phase of the cycle, others showed no change in weight and a few lost a pound or two.[2] Some who gained weight observed "tight, stuffy" feelings of body, hands and feet, diminished urinary output and increased thirst. Thorn, Nelson and Thorn described a tendency to gain weight not only at the time of the menstrual period but also at about the time of ovulation in the majority of 50 student nurses.[3] Premenstrual swelling of the abdomen, increased appetite and thirst were present more often among the subjects who showed a menstrual weight gain, but were sometimes reported by others as well. In a few subjects who underwent electrolyte balance studies, a decrease in the renal excretion of sodium was observed during the three days preceding menstruation, and also at the time of ovulation, when the output of estrin was increased. Following the onset of menstruation, there was noted an increase in the excretion of sodium and a reduction in body weight.

That these findings are of fundamental biologic significance is indicated by the work of Krohn and Zuckerman, who found that the body weight of female macaques may increase as much as 18 per cent at the time of menstruation.[7] Both the weight gain leading to "menstrual edema" and the various symptoms included under the term "premenstrual distress" have been thought to be due to sodium ion retention under the influence of ovarian steroids.[8] An increase in the steroids excreted by the adrenal cortex itself, on the other hand, has been postulated as the cause of the edema of pregnancy, preëclampsia and essential hypertension.[9, 10, 11] In view of the extremely close interrelationship and overlapping of function between the adrenal gland and the ovary which have been demonstrated experimentally, both ovarian and adrenal cortical activity should be taken into account in any consideration of the sodium metabolism of young women.[8, 12, 13]

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As part of a study of possible precursors of hypertension, we reported the effect of acute sodium withdrawal upon body weight in 83 normal young men.[14] Whereas the majority lost from one to three pounds of body weight following 24 hours of rigid sodium restriction, almost one quarter of the subjects failed to lose significant amounts of weight, and thus appeared to resemble hypertensive patients in their inability to excrete sodium.[15] Women were not included in the original experiment because it was thought that the fluctuations in weight associated with the menstrual cycle might make the results difficult to interpret. The present study was designed to observe both the cyclic fluctuations in body weight related to the menstrual cycle and the effect of acute sodium withdrawal in a group of normal young women. In this way it was thought that the rôles played by the adrenal cortex and by the sex hormones in the sodium and water equilibrium of women might be better understood.

Method

The observations were carried out on a group of 14 women medical students in good health, while they were pursuing their usual academic work. One of the subjects was Chinese. They ranged in age from 22 to 26 years, with a mean age of 23.7 years. The weights of nine subjects throughout the menstrual cycle lay within the range of "ideal weight" ± 9 pounds, as defined in the tables of the Association of Life Insurance Directors and Actuarial Society of America, 1912. Subjects 53W11 and 50W40 were overweight, $+17$ and $+13$ pounds, respectively, at their average weights, while subjects 51W15, 51W02 and 50W15 were underweight, -11, -12 and -19 pounds.

The first part of the experiment consisted in weighing each subject daily over a period of 35 consecutive days in October and November, ending just before the Thanksgiving holiday. Weights were recorded to the nearest 2 ounces * in the morning before breakfast, without clothes and after voiding.† Careful records were kept of the onset and duration of menstruation and of accompanying symptoms, if any. Special inquiry was made as to the presence or absence of headache, swelling, increased appetite, increased thirst or increased nervous tension. Daily notations were also made concerning general health and any unusual conditions. Bowel movements were recorded for each 12 hour period.

In the second part of the experiment, the same 14 subjects underwent duplicate sodium withdrawal tests between January 9 and March 10. The procedure and the composition of the sodium free diets were in general like those described for the men students.[14] The chief difference lay in the fact that on the two days preceding sodium withdrawal the subjects of this experiment ate their usual diets, with the customary amount of salt, rather

* In the tables ounces have been converted into decimals for convenience in calculating percentages.

† Weights thus obtained show a high degree of consistency.[14]

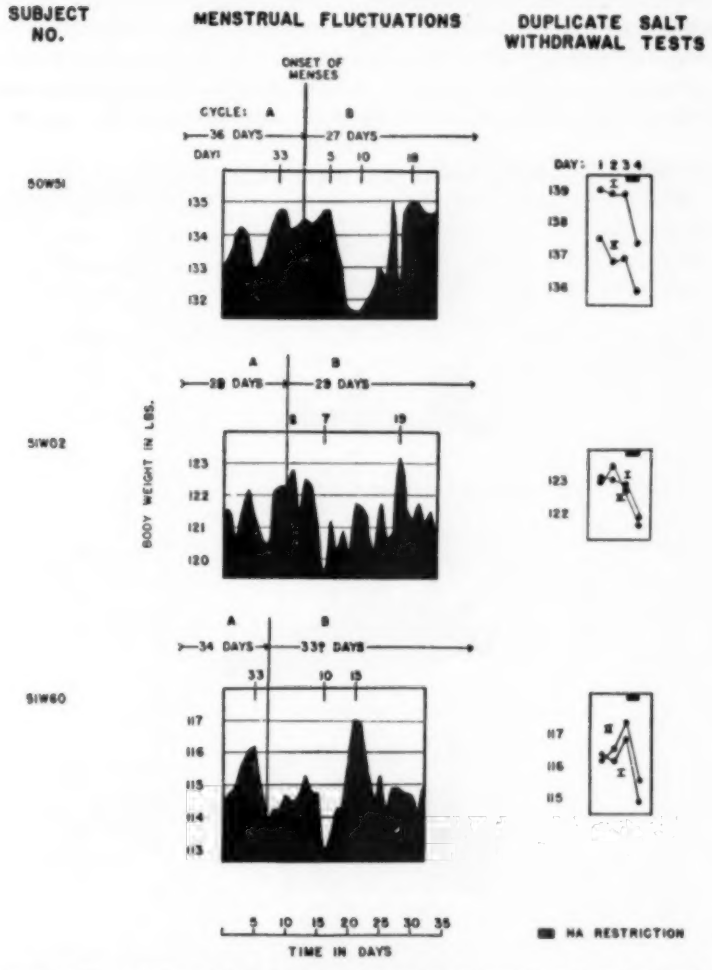

FIG. 1. Three weight profiles showing wide cyclic fluctuations and well defined intermenstrual peaks exceeding the menstrual peaks in height.

In figures 1 to 6 the fluctuations in daily weight of 14 normal young women are plotted with regard to their association with the menstrual cycle. The day of onset of menses, Day 1, is indicated by a vertical line. For easy reference, the exact days of maximal and minimal weight are indicated on the top line of each chart. Thus, subjects 50W51, 51W02 and 51W60 reached the point of minimal weight on Day 10, Day 7 and Day 10, respectively, of their menstrual cycles. The 35 day period of observation encompassed portions of two menstrual cycles, A and B; the total duration in days of each cycle is indicated.

The response of each subject to duplicate sodium withdrawal tests is charted to the right. Roman numerals indicate first or second test.

than the standard diet with salt added. Daily weights were recorded before breakfast from Tuesday through Friday mornings. Beginning on Thursday morning, the standard diet containing a total of 1 gm. of sodium chloride was given over a 24 hour period. Weight changes resulting from sodium restriction were calculated from the difference between the weights on

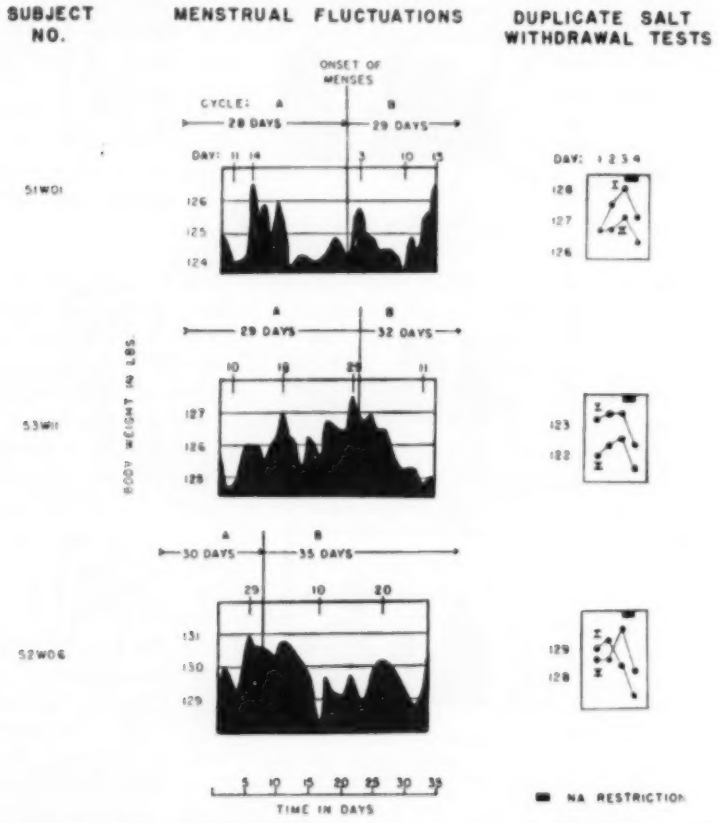

FIG. 2. Three weight profiles showing smaller cyclic fluctuations. The intermenstrual peak exceeds the menstrual peak in profile 51W01 but not in profiles 53W11 or 52W06. Note the similarity of the intermenstrual peaks in Cycles A and B in profile 51W01.

Thursday and Friday mornings. All tests were carried out on the same days of the week to avoid any effect from weekend changes in diet and activity.

The effect of sodium withdrawal upon the eosinophil count of five subjects was observed during the last week of the experiment. The total circu-

lating eosinophils were determined by direct count of blood taken from the finger just before lunch Thursday and Friday.[16] These five subjects ate salt-free breakfasts on Friday, so that the final counts were made after 29 hours of acute sodium restriction.

Results

A. *Weight Changes during the Menstrual Cycle:* The daily weight curves of the 14 subjects showed remarkable differences in appearance one from another. Variations in the degree and rapidity of the weight fluctuations produced distinctive individual patterns. Detailed curves of the subjects' daily weights are shown, because to the best of our knowledge com-

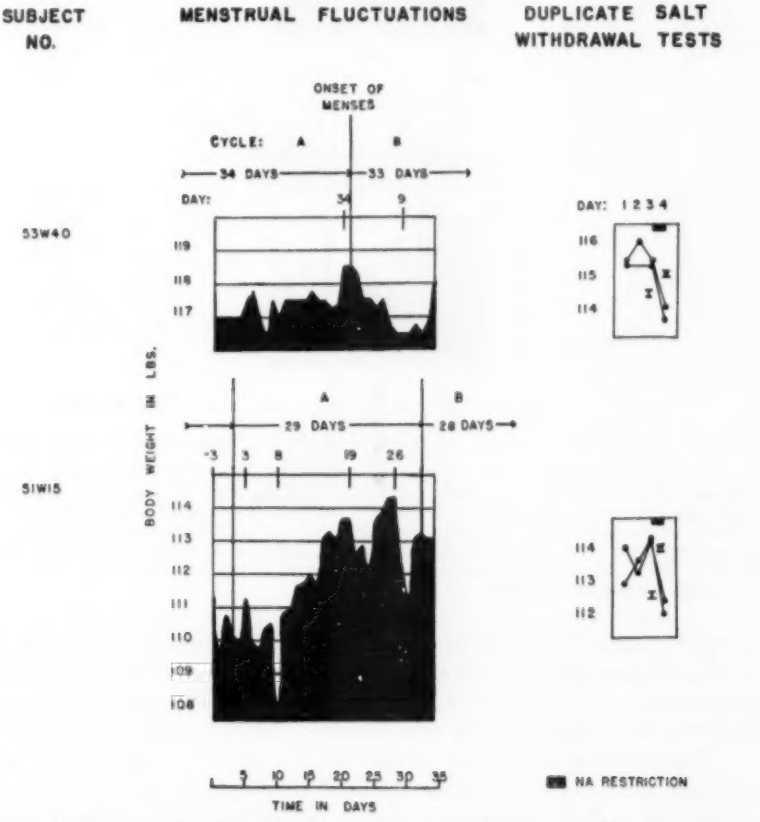

FIG. 3. The two weight profiles showing the smallest and the largest cyclic fluctuations; in these, the intermenstrual peak is less definite. Profile 53W40 shows suggestive peaks on Day 20 (Cycle A) and on Day 14 (Cycle B). Profile 51W15 shows a well marked peak on Day 19, only a week before what appears to be the menstrual peak.

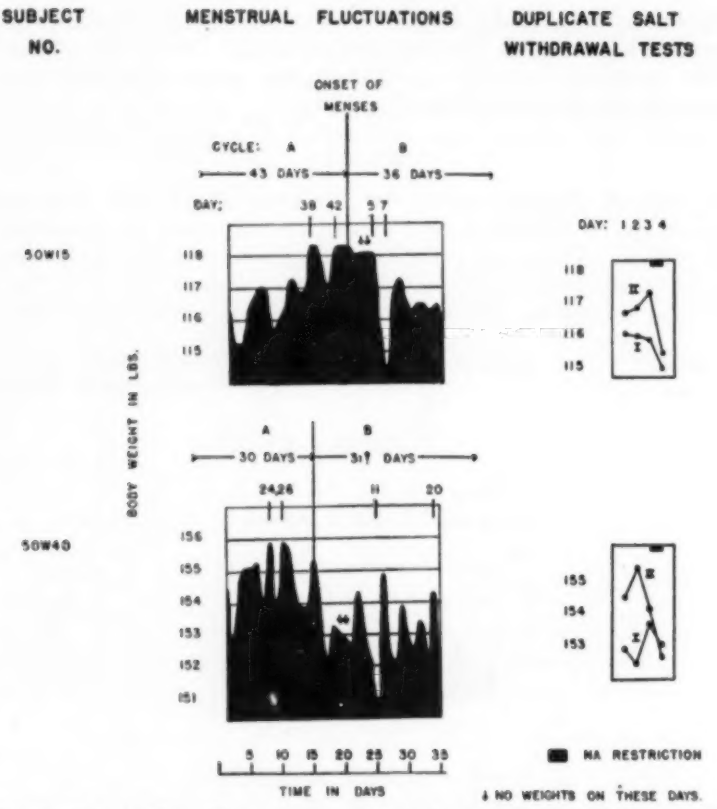

FIG. 4. Two profiles with contrasting patterns in regard to the rapidity of weight change. Profile 50W15 shows a series of curves with blunted tops where high weights were maintained for two or three successive days. The repeated finger-like projections of profile 50W40, on the other hand, indicate daily fluctuations in weight amounting at times to two pounds or more. The intermenstrual peak is not identified in either profile with certainty. Profile 50W15 began on the twenty-fifth day of an unusually long cycle (43 days), so that the usual intermenstrual phase was not observed.

parable charts have not appeared heretofore * (figures 1–6). In some subjects the weight curve profiles consisted of a series of sharp or fingerlike projections (51W02, 51W01, 50W40), while in others the patterns showed broader, blunt-tipped curves and plateaus (50W51, 52W06, 50W15).

Despite these individual variations in pattern, certain basic weight changes related to the different phases of the menstrual cycle could be identified. In general, the weight curves almost invariably showed peaks in

* The weights of four of Sweeney's subjects were plotted during the premenstrual and menstrual phase only.[2] Thorn et al. charted the weight of one subject for a month.[3] In both of these studies the subjects were weighed clothed.

close association with the onset of menstruation, which is indicated in the charts by a vertical line. In some subjects, well defined peaks lasting from 24 to 48 hours were observed just before (51W60), coinciding with (53W40), or just after (51W01) the onset of menses. Others showed a double peak with a high plateau of weight between (52W06, 50W51). The menstrual weight peak was followed by a sharp decline in weight, often becoming precipitous, to a point of minimal weight recorded shortly after

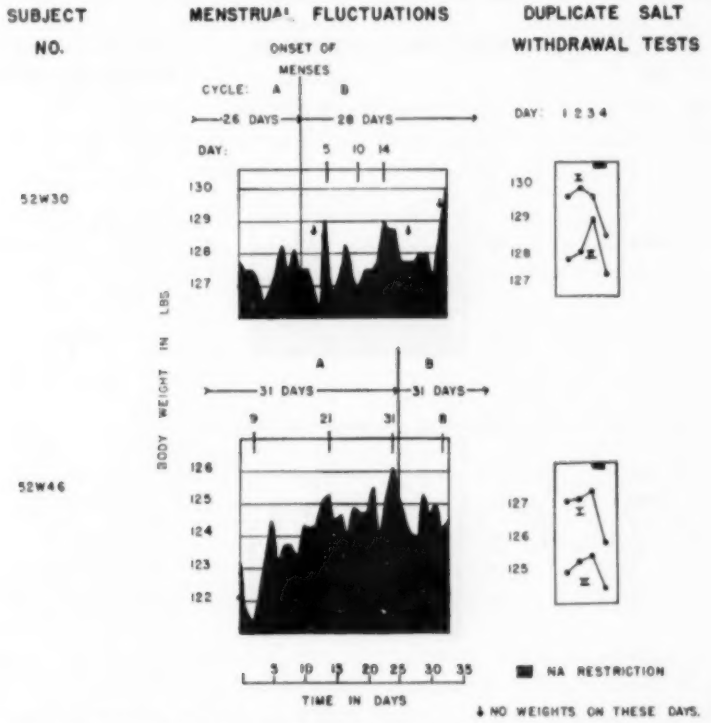

FIG. 5. Two irregular weight profiles. The highest peak in profile 52W30 occurred on Day 24 in Cycle B; no similar peak was present in the premenstrual phase of Cycle A. The points of low weight in Cycles A and B of profile 52W46 were quite different, and the identification of the intermenstrual weight peak as occurring on Day 21 is open to question.

the end of menstruation. A loss of 2 or 3 pounds of body weight within a period of several days often occurred at this time. The lowest point of the weight profile was reached between the seventh and twelfth days after the onset of menses in all but two subjects (52W30, 51W26). The duration of this postmenstrual phase of low weight was usually brief. After a day or two, weight gain recurred in a series of upward excursions, culminating in a second peak 14 to 21 days after the onset of menses.

In a few subjects similar points of high or low weight were observed to recur in successive cycles. Thus, subject 51W01 showed very similar intermenstrual weight peaks on Day 14 in Cycle A and Day 15 in Cycle B, as well as similar points of minimal weight on Day 11 in Cycle A and Day 10 in Cycle B. Unfortunately, the period of observation was too short to identify days of similar weight in many of the subjects with certainty. Moreover, in subjects 52W46, 51W26, 52W30 and 51W84 the weight patterns were quite irregular and difficult to interpret (figures 5 and 6).

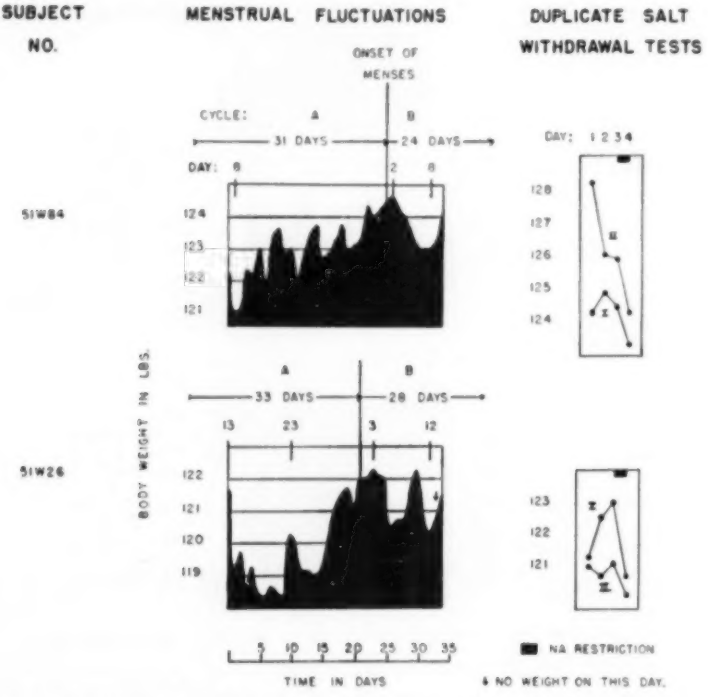

FIG. 6. Two irregular weight profiles. Like profile 52W46, profile 51W84 shows dissimilar points of low weight in successive cycles, and a series of similar weight peaks has replaced any single intermenstrual peak. In profile 51W26 the period of lowest weight occurs from Day 18 to 22 in the intermenstrual phase.

In view of these findings, the change in body weight associated with the menstrual cycle could only be approximately determined. It has been estimated in the 10 most regular subjects by obtaining the difference between the weight at the menstrual or the intermenstrual peak (whichever was greater) and the related point of minimal weight. The percentage change in body weight from the mean of these two weights was then calculated (table 1). Subject 51W15 showed the greatest fluctuation in weight,

amounting to 5.7 per cent of body weight, and subject 53W40 (the Chinese student) the least, or 1.7 per cent. The remaining eight subjects showed weight swings amounting to from 2.1 to 3.6 per cent of body weight.

Most of the subjects suffered from simple colds during the 35 day period of observation, and reported other variations in their daily lives ranging from loss of sleep to transitory changes in bowel habit. None of these conditions was persistent or serious enough to keep any subject from attending classes. The subjects with regular weight curves reported about as many of these minor stresses as did the subjects with irregular curves. None of the "unusual conditions" produced changes in weight which could be identified with certainty.

During the 35 day period of observation, 13 subjects experienced one or more of the symptoms about which specific inquiry was made, namely,

TABLE I

The Weight Fluctuation Associated with the Menstrual Cycle in 10 Normal Young Women

Subject	Maximal Weight	Minimal Weight	Cyclic Weight Change	
No.	Lbs.	Lbs.	in Lbs.	in %[3]
51W15	114.375 (M)[1]	108.000	6.375	5.7
51W60	117.000 (IM)[2]	112.875	4.125	3.6
50W40	155.875 (M)	150.750	5.125	3.3
50W15	118.375 (M)	114.500	3.875	3.3
51W02	123.125 (IM)	119.625	3.500	2.9
50W51	135.000 (IM)	131.625	3.375	2.5
53W11	127.500 (M)	124.750	2.750	2.2
52W06	131.000 (M)	128.250	2.750	2.1
51W01	126.500 (IM)	123.875	2.625	2.1
53W40	118.500 (M)	116.500	2.000	1.7

[1] Maximal weight at menstrual peak.
[2] Maximal weight at intermenstrual peak.
[3] Per cent of the mean total body weight.

headache, increased tension, increased thirst, swelling and increased appetite (table 2). In addition, three subjects reported breast tenderness. Symptoms were prominent in four subjects, each of whom experienced four or five symptoms for periods of up to six days. On the other hand, one subject had none of these symptoms, and in several others symptoms were inconspicuous. Headache was found to be the most frequent symptom. Although isolated instances appeared throughout the menstrual cycle, headaches were more frequent, more severe and more persistent during the week just before and the week just after the onset of menses (table 3). Subjects 51W15, 52W30 and 50W40 each suffered from three day headaches at some time between Day -3 and Day $+5$. Of a total of 33 headache-days reported by 10 subjects, 22 occurred between Day -7 and Day $+7$. Increased nervous tension followed a similar pattern, with two exceptions.

Subjects 51W60 and 52W46 both noted increased tension just before the point of lowest weight on Day +9. In four subjects increased thirst was present for periods of from two to six days between Day −5 and Day +6. Subject 51W84 observed this feeling on Day +9, and subject 51W60 on Days +14 and +15, just as she was reaching the intermenstrual weight

TABLE II
Symptoms

Subject No.	Headache	Increased Tension	Increased Thirst	Swelling	Increased Appetite	Breast Tenderness	Total
51W01	+	+	−	+	+	+	5
51W15	+	+	+	+	+	−	5
52W30	+	+	+	+	+	−	5
52W06	+	+	+	+	−	−	4
50W51	+	+	−	−	−	+	3
51W60	−	+	+	−	+	−	3
50W40	+	−	+	−	−	−	2
51W84	+	−	+	−	−	−	2
52W46	+	+	−	−	−	−	2
51W26	+	−	−	−	−	−	1
50W15	−	−	−	−	−	+	1
53W40	−	−	−	+	−	−	1
53W11	+	−	−	−	−	−	1
51W02	−	−	−	−	−	−	0
Total	10	7	6	5	3	3	

peak which, for her, was the highest weight of the month. Swelling was chiefly abdominal except in subject 53W40, who noted swelling of the feet only. Swelling occurred entirely during the premenstrual and menstrual weeks for periods of from three to six days. Increased appetite was never a conspicuous symptom among our subjects, usually occurring on but one

TABLE III

No. of Subjects Affected	Headache	Increased Tension	Increased Thirst	Swelling	Increased Appetite	Breast Tenderness
During Premenstrual and/or Menstrual Phases (Day −5 to +7)[1]	9	5	4	4	1	3
During Remainder of the Cycle	1	2	2	0	2	0
During Total 35 Day Observation Period	10	7	6	4	3	3

[1] In table 2 and in the accompanying text, time in days is counted in both directions from the observed onset of menses.

day. (Subject 51W01, Day −3; 51W15, Days +8 and +12; 52W30, Day +18; 51W60, Day +19.) Breast tenderness, on the other hand, tended to occur in close association with the onset of menses and to persist for some days. (Subject 50W15, Day −8 through +1; 50W51, Day −6 through −4; 51W01, Day −5 through +2.)

B. *Effect of Sodium Withdrawal upon Body Weight:* All subjects lost weight following 24 hours of sodium restriction in each of the duplicate tests (figures 1–6). The mean weight loss was 1.42 pounds for the first test and 1.35 pounds for the second test (figure 7). Calculated in percentage of body weight, the range of weight loss was from 0.41 to 1.97 per cent. The percentage weight loss of each subject in duplicate tests is given in table 4. In 12 subjects the consistency of the duplicate tests was good, with differences between the mean and the actual tests of less than 0.3 per cent of body weight. Only subjects 53W11 and 51W01 lost less than 0.9 per cent of body weight in both tests, and thus were "small losers," comparable

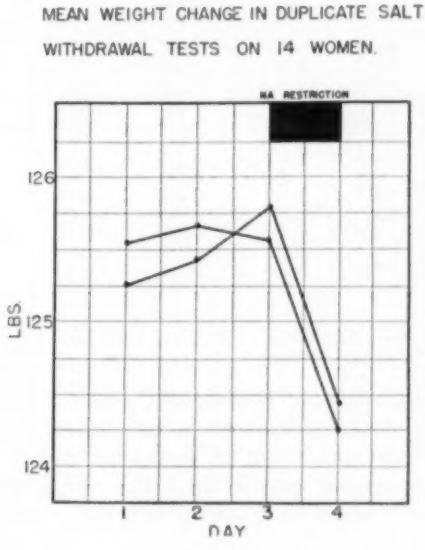

FIG. 7.

to the hypertensive patients of Perera and Blood.[15] The remainder of the subjects were either "large losers" or showed borderline responses.

The response to sodium withdrawal of this group of healthy young women was therefore strikingly similar to our results in young men.[14] Despite the fact that the basic weights of the young women were almost constantly fluctuating, often quite widely, the weight loss associated with sodium withdrawal was apparently neither masked nor exaggerated thereby. Although originally so intended, it did not often prove practicable to give the duplicate tests in the same phase of the menstrual cycle (table 4). Thus, subject 51W60 took the first test on Day 18 and the second test on Day 10 of the menstrual cycle, presumably in the postovulatory and preovulatory phases, respectively, with almost identical weight loss on the two occasions

(figure 1). Again, subject 51W15, who also showed similar losses of weight from sodium restriction, took the first test on Day 6 and the second test on Day 13, presumably *before* and *after* the day of minimal weight, respectively, so that her over-all basic weight might have been expected to be falling in one instance and rising rapidly in the other (figure 3).

TABLE IV

Percentage Loss of Total Body Weight Shown by 14 Subjects in Duplicate Sodium Withdrawal Tests Arranged According to the Degree of Consistency

Subject No.	% Weight Loss		Mean % Wt. Loss 2 Tests	% Difference Each Test from Mean	Day of Menstrual Cycle		Type of Response
	1st Test	2nd Test			1st Test	2nd Test	
51W01	0.684	0.590	0.637	0.047	20	8	Small loser
53W11	0.811	0.714	0.763	0.049	27	16	Small loser
51W60	1.709	1.580	1.644	0.065	18	10	Large loser
52W06	0.972	0.686	0.829	0.143	13	30*	Small loser
53W40	1.517	1.190	1.354	0.164	25	10	Large loser
50W51	1.080	0.731	0.906	0.175	19	13	Borderline
52W30	1.356	0.964	1.160	0.196	21	16	Large loser
51W15	1.532	1.967	1.750	0.218	6	13	Large loser
52W46	0.797	1.275	1.036	0.239	27	28*	Borderline
51W84	0.904	1.389	1.147	0.243	34*	9	Large loser
51W02	1.017	1.527	1.272	0.255	29(−1)†	28(−1)	Large loser
50W40	0.407	0.974	0.691	0.284	17	24	Borderline
50W15	1.493	0.755	1.124	0.369	28	19	Inconsistent
51W26	1.829	0.825	1.327	0.502	20	10	Inconsistent

* Premenstrual symptoms present.
† −1 = day before onset of menses.

C. *Changes in Circulating Eosinophil Count Following Sodium Withdrawal:* Although obviously incomplete, the observations that were made during this experiment concerning the eosinophil count are given in table 5. The initial count was made early in the period of sodium restriction rather than before it, which would have been preferable. The comparison in this

TABLE V

The Effect of Acute Sodium Restriction upon the Eosinophil Count

Subject No.	Initial per cu. mm.	Final per cu. mm.	Change in per cent
51W84	266	188	−30.1
52W30	172	128	−25.6
52W06	269	203	−24.5
50W15	459	369	−19.6
50W40	147	144	− 2.0

instance, then, is between a count made after five hours and one made after 29 hours of acute sodium restriction. The findings suggest that restriction of dietary sodium may often result in a decrease in the number of circulating eosinophils.

D. *Comparison of the Degree of Weight Change during the Menstrual Cycle with That Following Sodium Withdrawal:* In order to ascertain

whether a physiologic relationship exists between the degree of weight fluctuation during the menstrual cycle and the sensitivity of a given subject to acute sodium withdrawal, the weight changes under the two conditions have been compared. Therefore, the 10 subjects of table 1 whose cyclic weight fluctuations were regular enough to be measurable have been arranged according to the magnitude of the weight change observed during a single menstrual cycle, calculated in percentage of total body weight. The percentage weight change of the same subject following sodium withdrawal is given in the adjoining column (table 6). It will be seen that there is a similar trend in the magnitude of the two types of response in the same individual, although exceptions occur. Thus, subjects 51W15 and 51W60 showed the largest weight swings, both spontaneously during the menstrual cycle and following sodium withdrawal. Subjects 53W11, 52W06 and 51W01, on the other hand, who were the only three consistent "small losers" following sodium withdrawal, all showed much smaller and exceedingly similar weight swings during the menstrual cycle. The most conspicuous exception to the

TABLE VI

Subject No.	Comparison of Magnitude of Weight Change During Menstrual Cycle	Following Sodium Withdrawal
	%	%
51W15	5.7	1.8
51W60	3.6	1.6
50W15	3.3	1.1
50W40	3.3	0.7
51W02	2.9	1.3
50W51	2.5	0.9
53W11	2.2	0.8
52W06	2.1	0.8
51W01	2.1	0.6
53W40	1.7	1.4

general trend is seen in subject 53W40, the Chinese student, who, although exhibiting the smallest cyclic weight change, was a consistent "large loser" after sodium withdrawal.

Symptoms of premenstrual distress were not confined to subjects with striking weight fluctuations, as has been previously thought.[1] Comparison of tables 2 and 6 shows very little correlation between prevalence of symptoms and magnitude of weight change, either during the menstrual cycle or following sodium withdrawal. Thus, not only subject 51W15, whose weight swings were the largest, but subjects 51W01 and 52W06, who were "small losers" after sodium withdrawal, with relatively low menstrual weight peaks, each reported four or five of the tabulated symptoms (figures 3 and 2). Subject 51W02, on the other hand, who was symptom-free throughout the 35 days of observation, showed well marked peaks in her weight profile (figure 1). It seems clear that some factor other than retention of sodium and water plays a determining rôle in the appearance of the symptoms of premenstrual distress.

Discussion

These studies suggest that the degree of weight fluctuation associated with the menstrual cycle may be an index of fundamental endocrine patterns. It has been reported that certain individuals gain sufficient weight at the time of the menstrual period to produce edema while others do not.[2, 4, 17, 18] Our observations indicate that considerable difference does exist between individuals in this regard, since in our small group total body weight fluctuated nearly 6 per cent in one subject and less than 2 per cent in another—a threefold difference. There is reason to believe that most of the weight change is due to retention of sodium and water.[3] This belief is substantiated by the exacerbations of edema which have been noted in patients with congestive heart failure or nephrosis at the time of the menstrual period.[19, 20, 21]

The individuality of the weight curve profiles as to the duration, definition and relative prominence of the menstrual and intermenstrual peaks appears to reflect differences in the timing and intensity of several biologic rhythms. Cyclic weight fluctuations associated with menstruation are not yet fully understood.[22–26] They have been attributed to a reciprocal relationship between ovarian and pituitary hormones, which are alternately inhibited and released, with periodic secondary stimulation of adrenocortical hormone production.[22] The premenstrual weight increase comes at a time when the levels of estrogenic hormone and progesterone are too low to exert a direct sodium-retaining influence. On the other hand, estrogen oxidation products are plentiful, resulting in marked pituitary stimulation with concomitant increase in the activity of the adrenal cortex secondary to the release of adrenocorticotropic hormone.[26] Accordingly, the water and salt retention associated with the onset of the menstrual period probably results from sodium-retaining activity of the adrenal cortex.* The intermenstrual peak of weight occurs in association with a high titer of estrogenic substances in the blood, but there is probably a sudden increase of adrenal cortical activity at that time as well.[27] One may postulate that the point of lowest weight occurring between these two peaks represents the moment when, in a given individual, the resultant of the sodium-retaining effect of both adrenocortical hormones and estrogenic substances is at a minimum.

There is evidence that the degree of activity of the adrenal cortex governs the amount of body weight lost following acute sodium restriction.[28, 29] Our observations show that under comparable experimental conditions the ranges of weight loss in healthy young men and in young women are the same. There is no indication from our data that cyclic ovarian activity appreciably alters the behavior of the adrenal cortex in regard to its regulation of salt and water equilibrium. If anything, it would appear that under the stimulus

* A highly toxic protein known as "menstrual toxin," which may also be a pituitary stimulant,[23] is liberated into the blood stream at the time of menstruation. Urinary excretion of antidiuretic substance at the time of menstruation has also been noted, suggesting stimulation of the posterior portion of the pituitary gland as well.

of acute sodium restriction, the adrenal cortex dominates the situation to such an extent that cyclic weight fluctuations resulting from ovarian activity are to a large extent inhibited. Otherwise, it is difficult to explain the consistency of duplicate sodium withdrawal tests falling in different phases of the menstrual cycle.

From our limited observations, a parallelism seems to exist between the amount of weight lost following sodium withdrawal and that following the menstrual weight peak. A "large loser" in response to acute restriction of dietary sodium is also a "large loser" in response to a less well defined physiologic stimulus, occurring early in the menstrual cycle, which abruptly terminates the previous tendency toward retention of sodium and water leading to the menstrual weight peak. There are individuals, however, who do not lose significant amounts of weight under either circumstance. Evidence is accumulating that such a metabolic pattern, at least in response to sodium withdrawal, may characterize hypertensive and prehypertensive individuals.[14, 15, 30] If, as our data suggest, the degree of menstrual weight fluctuation parallels the sensitivity of a given subject to sodium withdrawal, more extended studies are indicated to determine whether adrenal cortical activity may not be the determining factor in each instance. The cyclic hormonal changes in women provide a unique opportunity for studying the human adrenal cortex in varying stages of physiologic activity. Not only changes in sodium and water equilibrium but also menstrual fluctuations in the number of circulating eosinophils, blood cholesterol and the glucose tolerance curve have been reported.[1, 4, 27, 31-34] A low point in blood cholesterol level and a glucose tolerance curve of the diabetic type have been found in normal women at the time of menstruation. The eosinophil count falls gradually during the premenstrual phase and shows a sudden decline at the time of ovulation. In this regard, observations on another healthy young woman, subject 50W42, not in the present group, showed several interesting features. Her first blood cholesterol level, taken routinely by the Bloor method, was 407 mg. per cent. Over a year later, the test was repeated. By chance, it was the first day of her menstrual period, while she was having abdominal cramps of moderate severity; her cholesterol level on that occasion was 228 mg. per cent and her total circulating eosinophils 47 per cubic millimeter. Several months later, when she was not menstruating, her blood cholesterol was 408 mg. per cent and her eosinophil count 131 per cubic millimeter. This subject was unusual in that she showed higher cholesterol values and a much wider range of fluctuation than any of the six women or 172 male subjects who have had two or more cholesterol determinations. Since cholesterol is probably a building stone for adrenal corticosteroids, such findings have considerable interest in terms of the equilibrium between the sex hormones and the adrenal cortex.[35, 36] This is particularly true in view of the extremely low incidence of coronary atherosclerosis in women as long as the menstrual function continues.

Young women are relatively free from the giant molecules of lipoprotein described by Gofman, and the electrophoretic pattern of lipoproteins of young women or of men receiving estrogenic hormones differs from the pattern of untreated male subjects.[37, 38] Whether these differences in cholesterol patterns are due to estrogenic hormone acting directly on lipoprotein substances, or indirectly through changing adrenocortical activity, has not yet been determined.

The studies here reported are clearly exploratory and by no means extensive enough to be conclusive. Before much more can be said as to the significance of menstrual weight fluctuations in terms of adrenal cortical activity, a group of young women should be studied for many consecutive months, preferably for a year, to determine which features of the individual weight curves remain relatively constant from month to month and which ones vary with changing environmental factors such as the season of the year.[39, 40] Consistent observations of the number of eosinophils and the level of cholesterol in the blood at specific points of the menstrual cycle should also be made. This is a difficult project, necessitating patience and the utmost coöperation on the part of the subjects, but, once accomplished, it might help to clarify ovarian-adrenal relationships, and to delineate hormonal patterns of etiologic importance in the development of essential hypertension and the toxemias of pregnancy.

Summary

1. Profiles of the daily weights of 14 normal young women have been charted during a period of 35 consecutive days.

2. Peaks of weight occurred in close association with the onset of menstruation and near the middle of the menstrual cycle, as noted by other investigators.

3. The point of minimal weight was generally found to occur from seven to 12 days after the onset of menstruation.

4. Following acute sodium restriction, the pattern of weight loss shown by the young women closely resembled the response of healthy young men previously described by us.

5. The mean percentage loss of total body weight among the women was 1.39.

6. The degree of consistency of the women's duplicate sodium withdrawal tests was the same as that found among the men.

7. There was no indication that menstrual weight fluctuations either mask or distort the response to sodium withdrawal.

8. The relative magnitude of the weight changes during the menstrual cycle and following sodium withdrawal in the same individual showed marked parallelism.

9. The significance of these findings in terms of endocrine equilibrium is suggested.

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* For the most part, these references have been selected to indicate what is known about normally functioning human beings. No attempt has been made to cover the vast amount of basic experimental work, references to which can readily be found elsewhere.

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ADVANCES IN ANTIBIOTIC THERAPY *

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Although the field of antibiotics is developing so rapidly as to render it almost kaleidoscopic, during recent months several topics of general interest have come into sharp focus. The subject of first consideration will include not only new drugs but also new forms of old drugs, as well as old drugs. Beyond this, I shall confine my discussion to two main items, bacterial resistance to antibiotics, and antibiotic toxicity.

New Antibiotics, and Old

Erythromycin (Ilotycin,† Erythrocin,‡) presently holds first place of interest in the evaluation of new antibiotics. Its history is a matter of record.[1] Although it seems to be finding its greatest usefulness as a well tolerated, orally administered alternate to penicillin in the control of gram-positive organisms, particularly staphylococci, it has a potentially broader field of effective use than penicillin (table 1), for it has been found efficacious in some cases of pertussis, as well as against rickettsiae and some viruses. We have had no extensive clinical experience with these latter organisms,

Table I

Erythromycin Effective

1. Gram-positives, including staphylococci and pneumococci
2. Gram-negatives, including gonococci and *Hemophilus pertussis*
3. Rickettsiae
4. Viruses

but against staphylococcal infections its effect has been quite satisfactory. Studies [2] by Finland and Haight have shown that, in a series of 500 staphylococcal strains resistant to penicillin, almost all were sensitive to erythromycin in vitro. Clinically, comparable results have been observed.[3] During the past several months at King County Hospital, a study of postoperative wound infections has been conducted in which 25 such strains of penicillin-resistant staphylococci were noted to have shown a good clinical response to erythromycin therapy. Likewise, in about 60 cases of bacterial pneumonia the clinical response of patients treated with this drug has been comparable in every respect to that observed in those treated with penicillin. The drop in temperature, the improvement in clinical condition, the complications and the mortality rate have been substantially the same.

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† Trademark, registered, Eli Lilly and Co.

‡ Trademark, registered, Abbott Laboratories.

Since the drug has become available in coated (acid-resisting) tablets, oral administration has given satisfactory blood levels (in the order of 2 to 6 micrograms/c.c.) within two to four hours,[3] and the administration of three to five of the 100 mg. tablets every six hours has maintained clinically adequate concentrations (averaging 4 to 10 micrograms, and occasionally reaching 20 micrograms/c.c.). These are higher levels than are usually achieved with aureomycin or terramycin. An intravenous preparation will be available soon, and administration of 0.5 gm. gives levels of approximately 20 micrograms/c.c. within a very few minutes, but these soon drop to the relatively low levels of 2 to 4 micrograms/c.c., so that intravenous administration probably should be repeated every two or three hours. Fortunately, the drug is so well tolerated by mouth that we have not had to resort to maintenance therapy by the parenteral route. The fact deserves emphasis, however, that the intravenous preparation has been very useful by permitting prompt initiation of treatment in patients who were vomiting.

Although untoward reactions have been few, one curious observation merits notation. Diarrhea has proved troublesome in some ambulatory patients, but has never been a problem in patients who were hospitalized while under treatment. The cause for this difference is unknown. Several patients have not tolerated the drug by mouth. One patient developed an eczematous rash in the folds of the skin, accompanied by considerable vaginal itching and burning and some diarrhea. This reaction was noted, however, after five days of effective drug therapy in an individual with bacterial pneumonia who had previously reacted violently to penicillin and the broad-spectrum antibiotics, and who had a long history of intolerance to all sorts of drugs. There has been no evidence of any urinary tract or hematopoietic toxicity, nor has any substantiated example of drug fever been seen. In fine, erythromycin seems to be a well tolerated and clinically effective antibiotic which undoubtedly will be very useful.

Carbomycin (Magnamycin *) has recently appeared upon the stage, but to date our personal experience with this drug is quite limited. While in vitro the level of activity of carbomycin is approximately the same as erythromycin, or less,[4] the blood and urine concentrations of the antibiotic are considerably lower.[5] Since the drug seems to disappear very rapidly from the blood even following intravenous administration (without concomitant rise in urinary excretion), it is postulated that carbomycin is very rapidly bound or otherwise rendered inactive by some element of the blood or tissues. It is reported to be especially effective against gram-positive organisms but to have little or no effect against gram-negative organisms.[6a, b] The one clinical report [7] which has appeared would indicate that it might possibly be useful in the management of urinary tract infections due to gram-positive organisms. Although it appears to have a low order of untoward reactivity, the place of carbomycin in the therapeutic armamentarium of the physician

* Trademark, registered, Chas. Pfizer and Co.

of the future will have to await more complete clinical and laboratory evaluation.

Of almost as much interest as the new antibiotics is the appearance of penicillin in at least two new forms. The first is a long-acting form, dibenzyl-ethylene-diamine dipenicillin G, to which the name benzethacil has been assigned (Bicillin *). It is reported to have maintained therapeutically effective blood levels as long as two weeks after the injection of a single 600,000 unit dose. Benzethacil is a well tolerated, tasteless substance which is effective by mouth as well as by the parenteral route. It apparently owes its prolonged activity following injection to its insolubility, which permits slow absorption. Balancing this prolonged activity from slow absorption, however, is the fact that the blood levels of penicillin are found to be quite low. Hence, parenteral use of this repository form of penicillin would appear to have its principal value in rheumatic fever prophylaxis and in the treatment of syphilis, rather than in the treatment of acute, severe bacterial infections. The second is the di-ethyl-amino-ethyl ester of penicillin, penethamate hydriodide (Neo-Penil †), which has the interesting property of accumulation in specific tissues. The original reports of this ester were most encouraging, and it looked as though at last there had been discovered a substance which might be of great value in the treatment of chronic suppurative lung disease.[8] The substance is reported to be inactive as administered. In the body it is filtered out or otherwise accumulated in considerable concentration in the lung tissue, pulmonary secretions, saliva and even in the spinal fluid, and is hydrolyzed into its active form (penicillin). However, it has not been possible to differentiate active penicillin and the inactive ester in lung tissue assays,[9] so that some investigators feel the initial optimism concerning its special value had best be tempered. In our hands, the clinical improvement of patients with lung abscesses to whom it was administered has not been spectacular. In fact, it seemed no more effective than procaine penicillin in comparable doses. Two cases of lung abscess and two cases of bronchiectasis, to whom procaine penicillin had been given for several weeks and in whom the pulmonary suppuration did not seem to be resolving, were given penethamate hydriodide. After a similar period of trial on this latter drug, little or no further improvement was noted: two came to surgery and two died. Recently a report [10] has appeared of three fatalities following the administration of penethamate hydriodide. As further reports of clinical trial of this substance appear in the near future, the question of its value should be answered. At present, one must approach its use with caution.

During the past year or two there has been a renewal of interest in Polymyxin B. This substance is undoubtedly the most effective agent against *Pseudomonas aeruginosa* (*B. pyocyaneus*). As originally isolated

* Trademark, registered, Wyeth Incorporated.
† Trademark, registered, Smith, Kline and French Laboratories.

and used, Polymyxin caused such severe renal damage as to preclude its further use. More recently, five different strains have been separated and, of these, Polymyxin B (Aerosporin *) has been found to have lower toxicity for the kidney while retaining its clinical potency. Light and his associates [11] compared Polymyxin A, Polymyxin B and a mercurial diuretic, and found that Polymyxin B produced only transient evidence of renal irritation. Since it is not absorbed from the intestinal tract, intramuscular administration is the route of choice for systemic infections. Daily dosage may safely approach 2.5 mg./kg. of body weight but should not exceed a 200 mg. total in any one day. Scattered reports are now appearing [12, 13, 14] which attest to both its clinical effectiveness and its lack of renal toxicity. Within the past month we have seen two pseudomonas bacteremias in which prompt, adequate use of Polymyxin B was undoubtedly lifesaving. With proper care and watchfulness for renal and nervous system toxicity, Polymyxin B has become a most useful and effective antibiotic in the control of those troublesome infections caused by *Pseudomonas aeruginosa.*

I should like to take this opportunity of reviewing with you once again the criteria which should be asked of the ideal antibiotic. This ideal has not yet been attained, but these characteristics should be fearlessly and fairly applied to the evaluation of each new antibiotic as it appears on the horizon:

1. Clinical effectiveness rapidly against the wide variety of pathogenic organisms.
2. Ready passage into all tissues and through all tissue barriers.
3. Ease of administration by oral and topical as well as parenteral routes.
4. Negligible toxicity.
5. Failure of susceptible organisms to develop resistance to it.

In any analysis of new and old antibiotics the question is usually raised as to what place can be found for new substances. How will it be possible to squeeze a new drug into an already crowded field? Recently, there appeared [15] a surprising answer in unequivocally practical terms, namely, the rate of commercial production of antibiotic substances. At that time, the monthly production of streptomycin and dihydrostreptomycin was rated at 21 tons, that of the "broad-spectrum" antibiotics, i.e., aureomycin, chloramphenicol and terramycin, at 24 tons, while penicillin was coming off the production lines at the rate of 30 tons each month!

Bacterial Resistance to Antibiotics

The resistance of bacteria to antibiotics has been an increasingly annoying problem.[16] Gonococci became resistant to sulfonamides, and colon bacilli early exhibited great resistance to streptomycin. In the field of tuberculosis, the emergence of streptomycin-resistant strains of tubercle

* Trademark, registered, Burroughs, Wellcome & Co., Inc.

bacilli at one time threatened the entire structure of drug therapy in this infection. Fortunately, with one major exception, this has not been true with penicillin. This one exception, however, bids fair to be an important one. It is the case of the penicillin-resistant strains of staphylococci. Evidence of this increase in resistance [17] can be drawn from the literature (table 2). A recent analysis of our own experience showed that 75 per cent of strains encountered at King County Hospital were penicillin-resistant. An appreciable proportion of these same strains were also resistant to aureomycin and terramycin and, to a lesser extent, to chloramphenicol [3] (table 3).

TABLE II

Increase in Penicillin-Resistant Staphylococci

		Percentage
1943	Spink	12
1945	Blair	21.5
1949	Nichols	68
1952	Kirby	75

It is pretty generally agreed that the cause of staphylococcal resistance to penicillin is the ability of various strains to produce penicillinase. Considerable argument has arisen, however, as to whether production of penicillinase is a characteristic acquired through adaptation to low concentrations of drug, whether it represents the emergence of mutants, or whether the strains were originally resistant due to their inherent ability to produce this penicillin antagonist. Work recently reported by Eagle suggests that slightly resistant strains represent adaptation to low concentrations of drug (such adaptation rarely being attained in stepwise fashion), while the very highly resistant strains represent spontaneous mutants.[18]

TABLE III

Staphylococci—King County Hospital, Seattle

	Per Cent Resistant
Penicillin	75
Aureomycin	40
Terramycin	40
Chloramphenicol	25
Erythromycin (Approx.)	0

It should be emphasized here that the strains reported generally represent hospital infections, such as postoperative wound infections, secondary pneumonias, gastroenteritis and urinary infections, and very likely indicate that we are developing inbred resistant strains for which our medical institutions and personnel are acting as reservoirs and carriers.[2, 17]

Putting aside contemplation of the intriguing problem of how resistance has evolved, one is constantly confronted by the problem of how to deal with patients who are ill with infections caused by such resistant staphylococci. In our hands it has been the practice to administer empirically and without

delay one of the broad-spectrum antibiotics, and, as indicated in table 3, this has usually been either chloramphenicol or, more recently, erythromycin. Sensitivity tests are carried out, and as soon as the results are known, if the patient is not responding satisfactorily, he is shifted to the appropriate compound as indicated by the in vitro tests. The great majority of our cases have responded to treatment with a single antibiotic. In a few, it has seemed advisable to consider combination therapy, and in these instances, combinations of penicillin with streptomycin or one of the broad-spectrum antibiotics have been tried, while occasionally combinations of antibiotics other than penicillin have been tried one with another. Rarely has such

TABLE IV

Therapeutic Groups of Antibiotic Combinations (Jawetz)

Group I	Group II
Penicillin	Aureomycin
Streptomycin	Chloramphenicol
Dihydrostreptomycin	Terramycin
Bacitracin	Probably sulfonamides

combination therapy offered better expectation of success than has the single-drug program.

I have avoided all discussion of antibiotic synergism and antagonism up to this point, for it is still a highly controversial topic and one for which sufficient data have not yet been produced to afford a clear-cut answer. (By definition, synergism means the attainment of an effect greater than would have been expected from simple summation of the activities of the drugs used.) The careful observations of Jawetz and his co-workers are well-known. He has recently summarized all this work [19, 20] by classing antibiotics into two groups (table 4). Jawetz feels that Group I compounds are

TABLE V

Clinically Effective Antibiotic Combinations

Enterococcus	Penicillin Streptomycin
Brucella	Aureomycin Streptomycin
Staphylococcus	Penicillin Bacitracin

generally synergistic, and almost never antagonistic, but occasionally indifferent. Group II compounds are generally neither synergistic nor antagonistic. When combinations of Group I and Group II compounds are used (and they must be used in such a way that at least one member of the combination is present in effective concentration), the Group II compound generally reduces the effectiveness of the Group I compound if the offending organism is sensitive to the Group I compound. On the other hand, the Group II compound may be expected to act synergistically with

the Group I compound if the organism in question is resistant to the Group I compound.[21] Table 5 gives several examples of clinically effective combinations which exhibit synergism.

The observations of Lepper and Dowling [22] on pneumococcal meningitis have afforded support for the conclusions of Jawetz just cited (table 6). In pneumococcal pneumonia, however, as reported by Ahern and Kirby,[23] this antagonism has not seemed to hold true. There was observed no evidence of antibiotic antagonism when they compared symptomatic improvement, temperature response, disappearance of pulmonary infiltration, length of hospitalization, complications and mortality in 50 cases, one-half treated with aureomycin and one-half treated with aureomycin plus penicillin. The several patients in each group whose temperature graphs suggested relapse actually represented secondary pneumonias, caused mainly by resistant staphylococci. These authors suggest that, while in pneumococcal meningitis there is significant interference with penicillin action by the broad-spectrum antibiotics, this is very probably a special instance, since in infections elsewhere in the body surface phagocytosis [24] is of such importance in

TABLE VI

Pneumococcal Meningitis (Lepper and Dowling)

Drug	Cases	Deaths	Mortality
Penicillin	43	13	30%
Penicillin and aureomycin	14	11	79%

aiding recovery that the slowing of penicillin's bactericidal activity by the other antibiotics is negated or relegated to a position of lesser importance. It would appear, therefore, that from the clinical point of view the future may reconcile more readily the current discrepancies between practical combination antibiotic therapy and theoretic concepts concerning antibiotic synergism and antagonism, as suggested recently by Dowling.[37]

TOXICITY OF ANTIBIOTICS

It seems like a far cry from the days of sulfapyridine and sulfathiazole treatment of infections, when one wondered if treatment would be effectively completed before the appearance of some severe drug reaction. Penicillin has been so relatively innocuous that most of us have been inclined to think of all antibiotics as being nontoxic. Suddenly last year the bubble burst, and we were rudely awakened by the great "to-do" about chloramphenicol. Dramatic discussion after dramatic discussion raged around the question of how toxic chloramphenicol actually was, and just what kind of toxicity one might expect from it. More heat than light was shed on the topic until Welch and his associates published the report of their survey.[25] In addition to aplastic anemia, cases of thrombocytopenia, anemia, granulocytopenia, agranulocytosis and pancytopenia were found. There seemed, however, to

TABLE VII

Blood Dyscrasias (Aplastic Anemia)—Welch et al., 1952

	Number	Deaths	Mortality
Chloramphenicol	55	23	42%
Chloramphenicol with other drugs	143	82	57
Chloramphenicol not involved	341	155	46
Totals	539	260	48%

be no relation among dosage, duration of treatment, severity of reaction, duration of reaction and mortality. Out of 539 cases of aplastic anemia collected in the survey, only 55 (10 per cent) occurred in patients who had had just chloramphenicol, while in 341 cases (62 per cent), the patients had not been exposed to the antibiotic in any form whatsoever (table 7). Furthermore, the mortality rate in the chloramphenicol group, although 42 per cent, was somewhat less than in the other groups. The question was also raised as to whether there had been a rise in incidence of aplastic anemia in the general population since the introduction of chloramphenicol. Unofficial figures [26] would suggest that such an assumption was not true (table 8). It is interesting to note that the estimated incidence of aplastic anemia among chloramphenicol-treated patients is less than in the general population.

TABLE VIII

Aplastic Anemia

Year	States	Case Rate
1949	30	1/240,000
1950	35	1/235,000
1951	36	1/270,000
Chloramphenicol patients		1/400,000

This figure is based on 8,000,000 patients, a very conservative estimate of the total number of individuals treated with this drug.

It appears, therefore, that there is a small but definite risk involved in the administration of chloramphenicol. Such a risk makes it advisable to use it only on clear-cut indication, to follow the patient carefully, and to stop therapy at the earliest sign of toxicity. Chloramphenicol is still a very valuable and very effective antibiotic, well-tolerated in the main. Its sphere of usefulness is quite definite (table 9). It is the drug of choice in the treatment of typhoid fever, and very frequently it is extremely valuable in the control of infections with other gram-negative organisms. Its value in staphylococcal infections which have proved resistant to penicillin therapy has already been mentioned. There is no reason to cast out this important

TABLE IX

Chloramphenicol—Indications

1. Typhoid fever
2. Proteus
3. Other gram-negative organisms
4. Staphylococcic infections

therapeutic agent; rather, it should be used with care and with recognition of its danger potential.

In the course of studying this problem of aplastic anemia, I reviewed the commonly recognized etiologic agents [27] and was quite surprised at what I found (table 10). This list again has impressed me with the well known fact that the use of every therapeutic agent carries with it a calculated risk.

Now a word or two about untoward reactions to other common antibiotics.[28] We all recognize as relatively unimportant many of the milder reactions,[29, 30] such as disturbances of the gastrointestinal tract with aureomycin, chloramphenicol and terramycin, involvement of the skin and mucous membranes, and serum-sickness-like disease with penicillin. Indeed, we accept the reasonably certain possibility of central nervous system involvement with streptomycin, and of renal damage with bacitracin. Less well recognized but still serious is the occurrence of anaphylactic shock with penicillin,[31] blood dyscrasias following streptomycin,[32] liver damage following parenteral aureomycin [33, 34] and exfoliative dermatitis with almost any one of our commonly used antibiotics. Kutscher and Lane [35] recently collected almost 100,000 reported cases of antibiotic-treated infections. While

TABLE X

Aplastic Anemia—Etiologic Agents

1. Benzene	6. Organic arsenicals
2. Gold	7. Anticonvulsants
3. Bismuth	8. Antihistaminics
4. Mercury	9. Sulfonamides
5. Atabrine	10. Streptomycin

the incidence of total reactions was not high (generally less than 1 per cent), if one considers the millions of patients who have been exposed to antibiotics in the past 10 years, an appreciable number of the citizenry have had toxic reactions to one or another of these compounds.

Another type of untoward reaction is being recognized,[36] which I will mention in passing merely to emphasize the simplicity of its recognition. I refer to the appearance of secondary invaders as a complication of what would otherwise appear to be adequate therapy. This may occur in either of two forms: (1) the overgrowth of other bacteria not inhibited or killed by the antibiotics being used, and (2) the appearance of fungus and yeast infections, such as moniliasis. From a practical standpoint, if a patient responds initially to treatment and then seems to relapse, appropriate cultures of blood, sputum, urine, etc., very frequently will show an entirely different offending organism, requiring a different antibiotic agent. This simply serves to emphasize my final point, namely that antibiotics are of tremendous value to us but are not without their dangers. They may extract an unexpectedly high price from our patients if we are not judicious in our use of the appropriate drug in the indicated infection.

Summary and Conclusions

1. New antibiotics (erythromycin and carbomycin), new derivatives of penicillin (benzethacil and penethamate hydriodide) and Polymyxin B have been discussed.

2. Methods of treating the increasingly frequent infections caused by penicillin-resistant staphylococci are mentioned.

3. The present status of the controversial question of antibiotic synergism and antagonism is summarized.

4. Consideration is given to antibiotic toxicity as it refers not only to chloramphenicol but also to the other commonly used drugs.

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OCCULT SUBACUTE BACTERIAL ENDOCARDITIS MANIFESTED BY HEMATOLOGIC ABNORMALITIES, INCLUDING PANCYTOPENIA *

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Anemia of variable degree is the commonest hematologic abnormality observed in subacute bacterial endocarditis. The erythrocytes are usually somewhat hypochromic but may be normochromic. Usually the leukocytes are normal in number, but they may be increased, particularly if embolic complications are present. Morphologically, "toxic" changes are apparent in the granulocytes, sometimes accompanied by a shift to the left. The number of platelets has not been consistently altered in cases reported in the literature. The presence of phagocytic reticuloendothelial cells in stained smears of peripheral blood has been demonstrated by many observers in about 15 per cent of cases. Although these cells have been found in other conditions, their presence in the blood suggests bacterial endocarditis. Sturgis [1] stated that phagocytic reticuloendothelial cells may be found in all cases of the disease if a thorough search is conducted by a trained observer.

Occasionally the hematologic picture may be more profoundly disturbed. Rare instances of pancytopenia, one of which is reported here, may be encountered in association with bacterial endocarditis. Such cases may lead to confusion in diagnosis by simulating a primary hematologic disorder. This report presents data on two cases (cases 1 and 2) in which the hematologic abnormalities overshadowed the "classic" manifestations of the disease to such an extent that the correct diagnosis was not established clinically. With modern methods of antibiotic therapy permitting cure in the majority of cases of subacute bacterial endocarditis, it is important to make this diagnosis correctly and as early as possible.

For years clinicians have been familiar with the maxim: "If the patient has a cardiac murmur and an unexplained fever, consider bacterial endocarditis." To this we would add: "If the patient has a cardiac murmur and an unexplained *anemia*, despite the absence of fever, consider bacterial endocarditis." Because of the few cases in which a murmur is an inconstant finding or is considered functional, still another maxim might be formulated: "If the patient has an unexplained fever and *anemia*, despite the absence of a convincing cardiac murmur, consider bacterial endocarditis." If the association of subacute bacterial endocarditis and hematologic abnormalities had been recognized, the following cases (which were difficult diagnostic problems) might have been resolved earlier with the correct diagnosis.

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Case Reports

Case 1. A Negro farmer, aged 44 years, was referred to the Mayo Clinic because of an indeterminate anemia for which he had received six transfusions, the last one having been given one and a half weeks before admission. Iron and liver had been administered without benefit. Predominant symptoms had been weakness and exertional dyspnea. He had lost 22 pounds in the preceding year. There was no history of fever, chills or sweats.

Arthritis involving the spinal column and peripheral joints had been present in varying degrees of severity for 15 years. After an examination 11 years previously, the patient had been told that his heart was enlarged. No other history of antecedent cardiac abnormality could be elicited.

On examination the patient was afebrile and had pallor of his mucous membranes. The heart was enlarged to the left. The cardiac rate was 116 per minute, with regular rhythm. A systolic thrill was felt which was maximal in the second left interspace 3 inches to the left of the midsternal line. A systolic murmur was heard over the entire precordium, loudest over the pulmonic area and along the left sternal border. Blood pressure was 100 mm. Hg systolic and 70 mm. diastolic. Chest expansion was markedly limited, and the spinal column was almost immobile. The spleen was not palpable. A psoriatic eruption was present in the scalp and on both lower extremities.

The hemoglobin concentration of the blood was 10.8 gm. per 100 c.c., the erythrocyte count 3,680,000 cells per cubic millimeter, and the leukocyte count 15,000 cells per cubic millimeter. A blood smear showed the anemia to be normocytic and normochromic; toxic granulation of the granulocytes was also noted. The sedimentation rate of erythrocytes (Westergren) was 56 mm. in one hour. The result of a Beck-Hertz test for sickling was negative. The urine was normal except for albumin, grade 2. A roentgenogram of the chest showed cardiac enlargement. Roentgenograms of the spinal column showed characteristic changes of rheumatoid spondylitis. Roentgen examination of the skull disclosed no abnormality. An electrocardiogram showed left axis deviation and inverted T waves in Leads III, V_1, V_5, and V_6.

Neurologic examination gave negative results when the patient was first seen at the clinic, but just prior to his hospitalization on the following day he noticed that his left arm and leg suddenly became weak. When examined at the hospital, he was found to have left facial weakness and hemiparesis. At the hospital he was seen in consultation by a cardiologist, who stated that the auscultatory findings were not particularly suggestive of a mitral valvular lesion, but the patient was near extremis at the time of the examination.

The patient remained afebrile with the exception of a single reading of 100° F. on the second hospital day. Two days after the onset of hemiparesis, bifrontal headache began and persisted for several days. Following this the patient became weaker and semicomatose. On the twelfth day he suddenly became apprehensive, hyperpneic and cold, and died within a few minutes.

Necropsy revealed subacute bacterial endocarditis of the mitral valve, which was the site of healed rheumatic endocarditis. The heart weighed 480 gm., compared to an average weight of 380 gm. for a man of this size. The myocardium contained multiple embolic abscesses. A large infarct was present in the right parietal lobe of the brain and another in the right kidney. The spleen weighed 525 gm. (normal, 150 gm.).

Comment: Although the findings in this case indicated the presence of organic heart disease, attention was focused on the unexplained anemia

which had for months dominated the clinical picture and proved refractory to treatment. In the absence of fever, cellular elements in the urine and a palpable spleen, the relation of the anemia to the cardiac findings was not recognized.

Case 2. A salesman, aged 46 years, was referred to the clinic because of weakness, loss of weight, dyspnea and purpura which had been present for three months. Eight months previously he had first experienced moderate dyspnea while walking through the snow and had had to stop several times within six blocks because of substernal constriction "like a vise." After that he had increasing exertional dyspnea and substernal constriction occurring also during excitement, aggravated by cold weather, and relieved by rest. Beginning three months before admission, he noticed general weakness and a further decrease in effort tolerance. His physician told the patient that he had heart trouble and anemia. The result of a bone marrow examination was said to be normal. The patient was hospitalized for 10 weeks and was given two blood transfusions as well as a number of injections of penicillin. After that he returned to work for four weeks but had to seek medical care again because of progressive weakness, dyspnea and substernal constriction. For the first time he noticed swelling of his legs, which gradually became severe. He also noted red spots on his feet and legs. A cough productive of brown sputum appeared. He estimated that he had lost between 10 and 15 pounds. There was no history of fever, chills or sweats.

On examination the patient was pale and moderately dyspneic after slight exertion. His temperature was 99° F., pulse rate 92 beats per minute, and blood pressure 104 mm. Hg systolic and 54 mm. diastolic. No adenopathy was noted. The heart was moderately enlarged clinically. Occasional premature contractions were detected. One examiner reported a faint systolic murmur at the apex, but subsequent careful examinations failed to confirm the presence of a cardiac murmur. Lung fields were clear. The liver was not palpable. The spleen extended 9 cm. below the left costal margin. Severe pitting edema was present in both lower extremities as high as the knees. Many purpuric spots of various sizes were found from the feet to the buttocks.

The hemoglobin concentration of the blood was 5.5 gm. per 100 c.c., the erythrocyte count 1,730,000 cells per cubic millimeter, and the leukocyte count 2,200, with a differential count of 24 per cent lymphocytes, 7 per cent monocytes, 67 per cent neutrophils, 1 per cent eosinophils, 0.5 per cent basophils and 0.5 per cent late myelocytes. A blood smear showed increased rouleaux formation and erythrocyte regeneration. The platelet count was 44,000 cells per cubic millimeter. Kline and Kahn reactions for syphilis were weakly positive, but further testing gave negative or doubtful results. Urine examinations showed specific gravity of from 1.005 to 1.009, with albuminuria, grade 2, and microhematuria, grades 1 to 2. Bence-Jones protein was not present. Urine cultures and smears revealed no acid-fast bacilli or other pathogenic organisms. The blood urea concentration was 66 mg. per 100 c.c., and the serum protein concentration 6.9 gm. per 100 c.c., with 2.6 gm. of albumin and 4.3 gm. of globulin. The serum contained 0.5 mg. of direct reacting bilirubin and 0.7 mg. of indirect reacting bilirubin per 100 c.c. Roentgen examination of the chest revealed cardiac enlargement, congestion of the pulmonary arteries and small adhesions at the base of the right lung. Roentgenograms of the skull and long bones were normal. An electrocardiogram showed a normal rate and rhythm, low amplitude QRS complexes in Leads I, II and III, and a diphasic T wave in Lead III. The precordial leads were within normal limits. Sternal marrow smears showed hypocellularity, with relatively active erythrocyte regeneration, moderate left shift in the myeloid line and a slight increase in plasma cells.

The findings suggested a primary hematologic disorder. The diagnoses most seriously considered were malignant lymphoma, myelosclerosis with agnogenic myeloid metaplasia, and subleukemic leukemia. On the third day of observation the patient's temperature reached 100° F. and on the fourth day it was 102.8° F. A roentgenogram of the chest at this time showed patchy areas of pneumonitis in the right lower and middle lung field. Penicillin was administered for four days, during which time the temperature returned to normal and remained normal. The patient was given four blood transfusions, a total of 2 liters of blood. After the transfusions his hemoglobin concentration was 5.0 gm. per 100 c.c., the erythrocyte count was 2,050,000 cells per cubic millimeter, and the leukocyte count was 3,100 cells per cubic millimeter. The platelet count was 58,000 cells per cubic millimeter. A tentative diagnosis of malignant lymphoma was reached, and four roentgen treatments were administered to the abdomen as a therapeutic test. The patient was dismissed 17 days after admission and instructed to return within four weeks for further evaluation.

Soon after returning home, however, the patient was hospitalized in another city, where he died 99 days after his initial examination at the clinic. During this period of hospitalization, no cardiac murmurs were heard and no blood cultures were performed. Necropsy revealed subacute bacterial endocarditis involving the mitral valve and, to a slight degree, the aortic valve. Congestive heart failure with congestive hepatomegaly and splenomegaly was present, as was focal glomerulonephritis. The latter complication was believed by the pathologist to be a terminal event.

Comment: This case shows the extreme difficulty encountered when subacute bacterial endocarditis is accompanied not only by anemia but also by leukopenia and thrombocytopenia, simulating a primary hematologic disorder. The pancytopenia was attributed to "toxic" suppression of bone marrow activity, since leukemic infiltration and the hyperplasia usually associated with hypersplenic states were absent. The rather marked splenomegaly was consistent with the tentative diagnosis of an abdominal lymphoma. The brief febrile episode was attributed to pneumonitis. The anginal distress was ascribed to coronary insufficiency resulting from coronary sclerosis complicated by the severe anemia. The thrombocytopenia seemed an adequate explanation for the purpuric lesions. The problem was further complicated by the fact that on only one occasion was a cardiac murmur heard by one observer, and repeated reëxaminations by several physicians failed to confirm this finding.

Although the patient was hospitalized and studied in three institutions, the diagnosis of bacterial endocarditis was not considered by any of the attending physicians, a fact which illustrates the confusion created by the existence of pancytopenia and the absence of many manifestations ordinarily associated with the disease.

While the occasional occurrence of leukopenia or thrombocytopenia has been noted, we are not aware of previous reports of pancytopenia in bacterial endocarditis.

Case 3. A white farmer, aged 60 years, came to the clinic because of weakness and loss of weight for two months and abdominal pain for two weeks. Past history was negative. The patient stated that he had lost 30 pounds in two months and had

become progressively weaker. He had been taking iron tablets for one and a half months, without apparent benefit. Two weeks prior to his examination at the clinic he had had two transfusions. For two weeks he had had a crampy, intense pain in his abdomen just under the right costal margin. The pain was worse at night, awakening him from sleep on numerous occasions. Neither coughing nor deep breathing aggravated the pain. There was no history of fever, chills or sweats.

The patient was pale and thin. The results of examination of the heart were negative. Over the anterior and lateral portions of his right lower chest there was impaired resonance to percussion, as well as diminished breath sounds and many râles. His epigastrium and right upper quadrant were tender on deep palpation. The liver was felt at the costal margin. His temperature on admission was normal. On the second day it was 101.4° F. The patient had not been aware of fever prior to admission.

The hemoglobin concentration of the blood was 10.8 gm. per 100 c.c., the erythrocyte count 4,390,000 cells per cubic millimeter, and the leukocyte count 13,400 cells per cubic millimeter, with a differential count of 15.5 per cent lymphocytes, 2.5 per cent monocytes, 79.5 per cent neutrophils, 1 per cent eosinophils and 1.5 per cent basophils. Blood smears obtained on several occasions showed a hypochromic anemia and left-shifted neutrophils which contained toxic granules. The sedimentation rate of erythrocytes by the Westergren method was 63 mm. in one hour. Examination of the urine gave normal results. A roentgenogram of the chest showed an inflammatory lesion at the base of the right lung. An excretory urogram showed no renal shadow on the left; the right kidney was enlarged and mild right ureterectasis was present. Cystoscopy and retrograde pyelography confirmed the presence of a solitary kidney. Culture of the urine gave negative results.

In the first week of hospitalization the patient first had a cough which was productive of thick, tenacious sputum. Bronchoscopy was performed with negative results. On the sixteenth hospital day the temperature, which had been normal with the exception of the reading noted previously, rose to 102° F. At the same time the patient had a rather sudden onset of pleural pain in the left lower portion of the chest and a chill. A roentgenogram of the chest at this time showed pneumonia at the bases of both lungs. Following the institution of chemotherapy, the patient's symptoms subsided and the temperature returned to normal. However, from that time the temperature reached levels of 100° to 101° F. on an average of two days in each week. Blood counts at this time revealed essentially the same findings as those recorded on admission. The patient was permitted to return home 38 days after admission.

He returned to the clinic two weeks later, having become stronger and remained at a constant weight. His temperature had continued to rise on one or two days of each week; the reading on admission was 100.6° F. Examination of the heart and lungs gave negative results. Roentgenograms of the chest were normal. The hemoglobin concentration was 8.5 gm. per 100 c.c., the erythrocyte count 3,960,000 cells per cubic millimeter and the leukocyte count 3,500 cells per cubic millimeter. The sedimentation rate was 43 mm. in one hour. Examinations of stools showed no evidence of occult blood or parasites. Urine examinations on several occasions gave normal results; cultures of the urine were sterile. Roentgen examinations of the entire gastrointestinal tract failed to reveal any abnormality.

The patient continued to have fever as high as 101° F. on one or two days of each week. The heart rate averaged 100 beats per minute. Three months after his first examination at the clinic, the patient was found to have a soft apical systolic murmur. Cultures of the blood were performed for the first time, and *Streptococcus viridans* was readily grown from all of three cultures. Another blood smear was examined and found to contain some monocytes with reticuloendothelial characteristics.

Comment: In this case the association of progressive anemia and fever, even in the absence of a cardiac murmur, might have suggested the diagnosis of subacute bacterial endocarditis. Although it is unusual for cardiac murmurs to be absent throughout most of the course of subacute bacterial endocarditis, this case and the preceding one illustrate that such an occurrence renders diagnosis difficult. A higher index of suspicion, resulting from the unexplained anemia, might have led to earlier performance of the appropriate studies by which the diagnosis was finally reached clinically in the last case.

The variations in the leukocyte count should also be noted. The leukocytosis present on admission was associated with a pulmonary complication which was probably embolic. Subsequent counts revealed a mild leukopenia. When a murmur was heard late in the course of the disease, cultures of the blood were performed and demonstrated streptococci. Reticuloendothelial monocytes were found in stained smears of peripheral blood at this time.

Platelet counts were not performed in this case. However, subsequent review of the blood smears made when the leukopenia was present revealed that the platelets were markedly reduced in number. Although we hesitate to report this as a case of pancytopenia without a more definite quantitative estimation of the number of platelets, the available evidence indicates that a pancytopenia was present at that time. Since the discovery of a murmur soon afterward led to establishment of the diagnosis and institution of antibiotic therapy, no further studies of the platelets were carried out.

General Comment

In 200 cases of bacterial endocarditis which we recently reviewed,[2] 75 per cent of patients were found to have anemia (hemoglobin concentration of less than 12 gm. per 100 c.c. in males, or less than 11 gm. per 100 c.c. in females). Anemia was present more frequently than evidence of embolization (61 per cent), splenomegaly (44 per cent), cardiac enlargement (37 per cent), and clubbing of the fingers (17 per cent). The incidence of anemia was equaled by that of fever (75 per cent), and was exceeded only by the findings of cardiac murmurs and bacteremia, both of which were present in 100 per cent of patients (table 1).

A comparison of the objective finding of anemia with the most frequent subjective symptoms is found in table 2. With the exception of a history of fever, no symptom was present in more than 50 per cent of patients. It will also be noted that the most frequent symptoms were constitutional, nonspecific manifestations. Furthermore, 38 per cent of patients gave no history of rheumatic fever or cardiac abnormality prior to the illness which proved to be bacterial endocarditis.

We were impressed by the fact that the manifestations classically associated with subacute bacterial endocarditis were present in a substantially

TABLE I

Bacterial Endocarditis: Comparison of Frequency of Anemia and "Classic" Manifestations in 200 Cases

Signs	Incidence, per cent
Cardiac murmurs	100
Bacteremia	100*
Anemia	75
Fever (temperature more than 100° F.)	75
Evidence of embolization	61
Splenomegaly	44
Cardiac enlargement	37
Clubbing of fingers	17

* Blood cultures performed in 197 cases.

smaller percentage of cases in our series than in previous reports in the literature based entirely on necropsy material. It is believed that our data, tabulated from clinical evaluation rather than from necropsy findings, represent more accurately the disease as seen by the clinician.

Twenty-eight patients (14 per cent) of our series had received treatment with iron, liver or blood transfusions before admission to the clinic. The diagnosis of bacterial endocarditis had been reached in none of these patients. Failure to establish the cause of the anemia probably delayed diagnosis and institution of proper treatment in the cases just mentioned.

Many patients have been seen in recent years after they have received one or more short courses of antibiotic therapy for a febrile illness which later proved to be bacterial endocarditis. By suppressing the fever and temporarily rendering the blood stream sterile, the antibiotic therapy masks two of the usual findings but does not cure the bacterial endocarditis. In the absence of fever, bacteremia and the less frequent manifestations of the disease, a soft systolic murmur might not be considered significant. Because of the frequent association of anemia and subacute bacterial endocarditis, one may not with assurance explain such murmurs on the basis of anemia alone. In view of these observations, hematologic abnormalities assume great importance in suggesting the diagnosis of bacterial endocarditis.

TABLE II

Bacterial Endocarditis: Comparison of Frequency of Anemia and Frequent Subjective Symptoms in 200 Cases

Manifestations	Incidence, per cent
Anemia	75.0
Fever (history of)	71.5
Loss of weight	41.5
Chills	33.0
Weakness	33.0
Fatigue	27.0
Sweats	22.5
Anorexia	18.0
Headache	15.0
Malaise	11.5
Dyspnea	11.0

Summary

Data have been presented on three cases which illustrate the difficulty in diagnosis which may arise when hematologic abnormalities overshadow the "classic" manifestations of subacute bacterial endocarditis. All three cases showed anemia, which we have found to be present in 75 per cent of cases of the disease. One case had pancytopenia which, to our knowledge, has not been present in any case previously reported in detail. It is emphasized that the association of a cardiac murmur and an unexplained anemia or of an unexplained fever and anemia should suggest the possibility of bacterial endocarditis.

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PROTEIN-BOUND BLOOD IODINE IN CARDIOVASCULAR DISEASE*

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Patients with cardiovascular disease accompanied by signs or symptoms suggesting hyperactive thyroid function are frequently encountered. In some instances, especially when goiter is present, careful study leaves an inconclusive clinical impression on which treatment is based. The deficiencies in the basal metabolism determination in evaluation of thyroid activity in hypermetabolic states of other origin prevent its being a decisive factor in differential diagnosis in some of these cases. This study was performed to learn whether the determination of the protein-bound iodine would provide a more satisfactory objective aid in diagnosis in such cases, so that proper cardiovascular treatment would be administered and uncalled-for antithyroid medication or surgery be avoided.

Others [1-11] have commented on the difficulty in clinically differentiating cardiovascular disease and thyroid disease. Turner [1] stated that clinicians were familiar with the difficulties sometimes experienced in distinguishing between cases of hyperthyroidism and hypertensive vascular disease, particularly when the basal metabolic rate was elevated, and that no satisfactory information on the blood iodine in hypertensive vascular disease was available. Curtis and Swenson [5] reported that essential hypertension and varying degrees of cardiac failure were frequently found in association with nodular goiter, and that thyroidectomy, undertaken when such complicating diseases were not clearly differentiated and under optimal control, might prove disappointing. They listed hypertension and organic heart disease with other conditions which might mimic hyperthyroidism. Noehren [9] reported that, of a series of 1,000 cases referred with the diagnosis of some thyroid disorder, 18.5 per cent showed no involvement of the thyroid gland. One hundred forty-nine of these cases fell under four diagnoses: neurosis, organic heart disease, neurocirculatory asthenia and hypertension.

Rose [7] reported that the diagnosis of hyperthyroidism should be made with extreme caution in the presence of persistent diastolic hypertension, and that this condition was the most important to separate from hyperthyroidism, especially when accompanied by tremor, tachycardia, increase in the basal metabolic rate and weight loss. Boas and Shapiro [6] reported that cases in which diastolic hypertension and increased basal metabolic rate coexisted were not rare, and that these cases represented a special syndrome

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which should be differentiated from hyperthyroidism as well as from the ordinary form of essential hypertension.

Salter [4] reported seven cases of cardiac decompensation in which the protein-bound iodine was useful in evaluating thyroid status when the basal metabolic rate was elevated. He felt the determination was particularly helpful when the elevation was due to cardiac decompensation. Curtis and Fertman [12] stated that the level of the protein-bound iodine may be useful in differentiating hyperthyroidism from other similar conditions in which the basal metabolism is elevated; as, for example, in patients with hypertension or cardiac decompensation. Curtis and Fertman [11] reported a group of 28 cases of cardiovascular disease in which whole blood iodine studies were done. McCullagh [13] reported three cases in which determination of the total blood iodine was useful in ruling out hyperthyroidism. Bruger and Mobius,[14] reporting on 44 cases, concluded that the mean values of whole blood iodine were increased with hypertension. Paal [15] reported that many hypertensives had very high whole blood iodines; the increase was not found with regularity, however, since it appeared in only 11 of 25 cases of hypertension studied. Kisch [16] reported that the blood iodine of cardiovascular disease fell within normal limits, even though the basal metabolism might be increased. He reported 28 cases of cardiovascular disease, and concluded that the whole blood iodine would be normal in cardiovascular disease but elevated in hyperthyroidism. Davidson [17] reported four cases of cardiovascular disease with normal protein-bound iodine, and felt this might be a means of differentiating uncomplicated cardiovascular disease from hyperthyroidism.

Starr et al.[18] reported that blood iodine studies were performed as part of the evaluation of many cases of congestive heart failure of obscure etiology. They presented 30 cases, and concluded that the test would disclose instances of thyroid disease usually unrecognized, and that the routine use of the test was well warranted by the clinical results.

Swenson [19] reported six patients with nodular goiter, hypertension and elevated basal metabolic rates, with low or essentially normal protein-bound iodine levels, and thus felt that the protein-bound iodine was a useful aid in the differentiation of hyperthyroidism from those entities which may mimic it.

Hallman et al.[20] reported a case of congestive heart failure accompanied by hyperthyroidism and one accompanied by myxedema, and stated that the protein-bound iodine made the diagnosis possible in each case.

Silver et al.[21] after studying 100 cases of hypertension, polycythemia, leukemia, lymphoma, Paget's disease and other states, reported that in hypermetabolic states not due to hyperthyroidism the function of the thyroid gland was normal as measured by the level of the protein-bound iodine and the urinary excretion of I^{131}.

From these reports it is inferred that a problem frequently exists in the

differential diagnosis of cardiovascular and thyroid disease; that no specific means is in widespread use for making this differential diagnosis; that the basal metabolism determination is often inadequate for this purpose, and that patients are occasionally submitted to procedures the results of which are disappointing because of the difficulty in ruling out thyroid disease in patients with cardiovascular disease. Prior to the report of Silver et al., no appreciable series of cases was found which had been made the basis for study of the value of the protein-bound iodine in the differential diagnosis of cardiovascular disease and other hypermetabolic states from hyperthyroidism. Those reports based on whole blood iodine values are of little value in this regard since the significant fraction is the protein-bound iodine,[22] which presumably represents, physiologically if not chemically, the circulating thyroxine of the blood.[23, 24]

Method

The method used during this study involved the modified Chaney still, and was similar to that reported by Barker,[25] Taurog and Chaikoff [22] and Connor et al.[26] The procedures and apparatus were modified to fit our laboratory facilities. The room in which the determinations were run was kept free of iodine at all times. A mechanical exhaust was used in place of a hood for removal of fumes (Curtis). A Klett-Summerson photocolorimeter was used for the colorimetric determination. The procedure consisted of precipitating the organic material of the blood with Somogyi's reagent, washing the precipitate with distilled water to remove any inorganic iodine; digesting the organic material with chromic oxide and sulfuric acid; reducing with phosphorous acid; distilling the volatile iodine substance into potassium hydroxide solution, and measuring the iodine colorimetrically by its catalytic effect on the reduction of ceric sulfate by arsenous acid.

Results

Nine hundred forty-seven protein-bound iodine determinations on 842 patients were made during the period covered by the study. In evaluating results, the final diagnosis made in all cases was accepted as the one to be used for classification purposes. Material for the study included cases from local hospital out-patient clinics, in-patients at one hospital, patients from private practice, and patients referred by physicians for the determination only.

Table 1 presents the distribution of the cases of cardiovascular disease or thyroid disease encountered during the period of the study. A total of 160 cases is included.

Of these 160 cases, 49 were clinically confusing in evaluating the part played by thyroid activity in the clinical state which existed. In these 49 cases the protein-bound iodine was of value in reaching a final decision in

TABLE I

Distribution of Cases

Hypertensive vascular disease	105	
Malignant hypertension		4
Arteriosclerotic heart disease	24	
Syphilitic heart disease	1	
Rheumatic heart disease	3	
Renal disease with hypertension	3	
Hyperthyroidism	15	
Associated with vascular disease		12
Hypothyroidism	9	
Associated with vascular disease		5
Hyperthyroidism considered but not final diagnosis		22
Hypothyroidism considered but not final diagnosis		2
Total	160	

41. In five cases it was below and in three it was above the level considered consistent with the final diagnosis. Twenty-five of these 49 cases had goiter in some form.

Table 2 records the number of determinations of protein-bound iodine and of basal metabolic rate done on the patients with cardiovascular disease and thyroid abnormalities. In the euthyroid group, 33⅓ per cent of the basal metabolic rate readings were above plus 15, and 16⅔ per cent were below minus 10; in this group, 19 per cent of the protein-bound iodines were above a normal high of 9 micrograms per cent, and 5.5 per cent were below a normal value of 3 micrograms per cent. In the hyperthyroid group, 83 per cent of the basal metabolisms were in the high range and 17 per cent in the normal range; 65 per cent of the protein-bound iodines were in the high range and 35 per cent in the normal range. Many of the basal metab-

TABLE II

Type of Case	Protein Bound Iodine			Basal Metabolic Rate		
	Normal	High	Low	Normal	High	Low
	(Total Number of Determinations)					
Apparently euthyroid	97	24	7	21	14	7
Hyperthyroid	18	33	0	6	30	0
Hypothyroid	13	0	6	3	0	5
Original impression, hypermetabolism; final impression, normal	25	1	1	3	8	0
Values after treatment	6	1				
	159	59	14	33	52	12
	Total 232			Total 97		

olism records were actually unsatisfactory single records showing poor breathing or excitement which, ideally, should have been repeated; this fact makes conclusions difficult to draw from the basal metabolism figures. In the hypothyroid group, 13 out of 19 protein-bound iodine determinations gave values below 4 gamma per cent. In the hypothyroid patient, both the basal metabolism and the protein-bound iodine would appear to correspond fairly well to the clinical impression.

In that group of patients in whom the original clinical impression was hypermetabolism, possibly of thyroid origin, but the final diagnosis was a euthyroid state, 25 of 27 determinations of the protein-bound iodine fell within the normal range. In this same group, eight of 11 basal metabolism determinations fell within the range of hyperthyroidism. It is interesting to note that in seven instances where the protein-bound iodine was determined after surgical or medical treatment of hyperthyroidism, it had fallen in every case significantly from the previous elevated levels, which is the expected response.

It was found that the values for the protein-bound iodine in cardiovascular disease cases corresponded very closely to the curve of distribution of the protein-bound iodine in the total number of cases included in the study. The values obtained in hypothyroidism were definitely shifted to the low range and for hyperthyroidism to the high range. An appreciable overlap occurred, and the determination cannot replace the total evaluation of the patient, but is a useful and practical aid.

Values for protein-bound iodine on patients who had more than one determination, made either as duplicates or within 10 days, which should alter the values little,[27] showed an average variation of 1.96 micrograms per cent; the average variation of the duplicate determinations only was 1.06 micrograms per cent; this latter figure is within the range generally acceptable for clinical use [18, 29, 30]; the former figure includes all values, even where large variations occurred which were obviously of technical origin.

Forty-two cases, representing 47 determinations, were available from laboratory personnel or euthyroid patients for controls. Five of these cases had values above the upper level considered normal, and one below the lower level. The high group contained one case of pregnancy, which may give an elevated protein-bound iodine.[21]

Summary

1. The differential diagnosis of some cases of cardiovascular disease and thyroid disease may be difficult.

2. Results of the determination of the protein-bound blood iodine in 160 patients with cardiovascular disease are reported.

3. The protein-bound blood iodine in cardiovascular disease tended to fall within normal limits. Values above or below the normal range oc-

curred in a frequency similar to those found in a large group of in-patients and out-patients of a general hospital.

4. The protein-bound blood iodine in hyperthyroidism is above the normal range, and the normal level of this substance in hypermetabolic states of other origin, particularly in cardiovascular disease, makes this determination a useful aid in differential diagnosis.

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EXPERIMENTAL HYPERTENSION *

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Experimental hypertension has made three useful contributions to clinical medicine: insight into the possible pathogenesis of essential hypertension, explanations for our therapeutic failures, and opportunities for the development and perfection of new methods of treatment. The basis for these relationships is perhaps best illustrated by a comparison of human hypertension with the principal varieties of the experimental disease.

Although the blood pressure can be increased in animals by a great number of methods, consistent and sustained elevations have been associated with three major types of experimental hypertension: (a) neurogenic; (b) renal, and (c) desoxycorticosterone acetate (DCA)-induced.

Neurogenic Hypertension

Neurogenic hypertension is produced by cutting the right and left aortic and carotid sinus nerves, which together constitute the moderator group. Although these nerves had been previously described, the first man to appreciate their fundamental importance for blood pressure regulation appears to have been Hering in 1924.[1] The demonstration that chronic hypertension may follow their section was made by Koch and Mies in the rabbit in 1929 [2] and by Heymans and Bouckaert in the dog in 1931.[3] The blood pressure rises immediately after the last nerve is cut, but soon reverts to or toward the preoperative limits. After a period of two or more days a secondary elevation occurs. The pressure then usually continues to increase for several months.[4, 5, 6] The degree of elevation may be extreme (as high as 425 mm. Hg systolic and 222 mm. Hg diastolic),[4] and is usually correlated with a corresponding increase in heart rate.[4, 7] The dominant functional change in neurogenic hypertension is a large increase in the cardiac output,[7] although the peripheral resistance may be increased somewhat.[8] Little change has been found in renal function,[6, 7, 9] although some rise in renal arteriolar resistance may occur.[7] Pathologically, this type of hypertension is characterized by a greatly enlarged heart [10, 11, 12] with little alteration of kidney structure.[4, 9]

Renal Hypertension

A procedure for consistently inducing renal hypertension was first reported by Goldblatt in 1932.[13] The technic consisted of partially constricting one or both renal arteries with metal clamps, producing a variable degree of renal ischemia.[14] With this procedure, some rise in blood pressure may be

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demonstrated within a few hours,[15, 16] but as a rule the greatest elevation does not occur for a period of several weeks.[14]

The dominant functional alteration in this variety of renal hypertension is a rise in peripheral resistance,[17] without material change in cardiac rate [14, 18] or output.[17] Abnormalities in kidney function vary with the degree of renal arterial constriction, from no demonstrable change,[19, 20, 21, 22, 23] even in renal blood flow, [20, 23] to marked reduction in all functions,[14, 24] terminating in fatal uremia.[24] Pathologic findings include moderate cardiac hypertrophy [25, 26, 27] and varying degrees of arteriolosclerosis,[14, 25, 28] hyalinization and necrosis.[29, 30] These arteriolar changes are absent from the clamped kidneys, even in the presence of advanced lesions elsewhere.[29] If but one renal artery is constricted, typical lesions occur in the arterioles of the contralateral kidney.[30]

An alternative method of producing renal hypertension is to enclose the kidneys in cellophane, silk or latex envelopes, as first demonstrated by Page in 1939.[31] With this technic, three to five weeks elapse before marked elevations of pressure occur, corresponding to the time required for the formation of a fibrous shell around the kidney.

Renal hypertension can also be induced by removing one kidney and tightly constricting the other by means of a figure-of-eight ligature around the poles, as demonstrated by Chanutin and Ferris in 1932.[32] Grollman modified this procedure in 1944 by using ligatures around both kidneys.[33]

In the early stage of hypertension induced by renal arterial constriction, the kidney releases in excess an enzyme called renin,[34] which in turn acts on a constituent of the alpha$_2$ globulin fraction in blood, called renin-activator or hypertensinogen,[35, 36] to form a new substance, hypertensin or angiotonin, which is a pressor material.[36, 37, 38] Although renal hypertension tends to persist indefinitely, renin and hypertensin are present in the blood of such animals only transiently.[39] The exact nature of the pressor mechanism in the later stages of renal hypertension is incompletely known.

Although the various methods of producing renal hypertension are commonly assumed to involve the same initial mechanism, namely, renal ischemia with release of renin, definite proof of this hypothesis is lacking.

Desoxycorticosterone Hypertension

The ability of desoxycorticosterone acetate (DCA) to induce hypertension was first demonstrated by Selye in 1943.[40] Following the repeated injection of DCA in oil, or the implantation of DCA pellets, a significant rise in blood pressure can be demonstrated in about one week, although the attainment of maximal hypertensive levels usually requires three to six weeks.[41]

If DCA is administered in small doses for brief periods (for example, two weeks), the blood pressure tends to return slowly to normal when administration of the drug is stopped. If larger doses are given for longer

periods, a stage may be reached in which the hypertension becomes permanent in the complete absence of further DCA administration.[42, 43, 44] This self-sustained post-DCA disease is characterized pathologically by cardiac and renal hypertrophy and diffuse arteriolosclerosis, most evident in the kidneys.[44]

TABLE I

The Effects of Various Agents and Procedures on the Blood Pressure in Experimental and Essential Hypertension

Agent or Procedure	Neurogenic	Renal	Post-DCA	Essential
Hypophysectomy	Unknown	Variable reduction	Reduced to normal	Unknown
ACTH	Unknown	Restored in hypophysectomized animals	Slightly increased	Slightly increased
Adrenalectomy	Unknown	Reduced to normal	Unchanged	Some reduced, most unchanged
Cortisone	Unknown	Increased under some conditions	No effect	Slightly decreased; increased if renal disease present
DCA	Unknown	Increased or no effect	Increased	Increased
Thyroidectomy	Unknown	No effect	Reduced transiently	Little effect
Thiouracils	Unknown	Unknown	Reduced transiently	Little effect
Thyroxin—Thyroid	Unknown	Increased in hypophysectomized animals	Slightly increased	Little effect
Parathyroidectomy	Unknown	No effect	No effect	Unknown
Calciferol—Calcium	Unknown	Unknown	Slightly increased	Unknown
Gonadectomy	Unknown	No effect	No effect	No effect
Testosterone	Unknown	No effect	Unknown	Little or no effect
Estrogens	Unknown	No effect	Unknown	Occasional small reduction
Nephrectomy	No effect	Reduced to normal (may not in rats)	Reduced to normal	Unknown
Sodium Depletion	Unknown	No change in dogs. Sometimes reduced in rats	Unchanged	Some reduced, most unchanged
High Sodium Intake	Unknown	Increased or no change	Little change	Slightly increased
Potassium Depletion	Unknown	Reduced toward normal in rats	Unchanged	Unknown
Barbiturates—Sleep	Reductions to normal with sleep	Variable effect; reduction late in the disease	Variable, transient reduction, to normal in some	Variable, transient reduction, to normal in some
Blocking Agents—Dibenamine	Exaggerated reduction	Small, variable reduction late in the disease	Variable, transient reduction	Variable, transient reduction
Sympathectomy	Abolished	No change	Unknown	Some reduced, most unchanged

A comparison of these three major types of experimental hypertension with essential hypertension shows many provocative similarities and certain important distinctions. Of particular interest is the influence of the nervous system, the endocrine glands and the kidneys, as well as the effects of drugs and diet (table 1).

Influence of the Endocrine Organs

So far as is known, three glands appear to have little to do either with the three major types of experimental hypertension or with essential hypertension itself. These glands are the thyroid, the parathyroid and the gonads. Insufficiency produced by their removal or inhibition,[44, 45, 46, 47, 48, 49, 50, 51] or hyperactivity produced by administration of their secretory products in large quantities,[44, 48, 51, 52, 53, 54] in most cases produces only small and variable changes in blood pressure.

By contrast, hypophysectomy produces a variable but large reduction in renal hypertension,[55, 56] prevents DCA-induced hypertension,[57, 58] and is followed by a slow recession to normal pressures if performed after the post-DCA hypertensive syndrome has become established.[44, 58] The effect of hypophysectomy in neurogenic hypertension, as in essential hypertension, is unknown.

Adrenocorticotropic hormone (ACTH) slightly augments post-DCA hypertension[58] and essential hypertension.[59, 60] ACTH also reverses the effects of hypophysectomy in renal hypertension,[61] but does not restore the ability of DCA to induce hypertension after the pituitary has been removed.[57]

The effect of adrenalectomy in most cases of renal hypertension is a reduction in pressure to normal.[47, 62, 63, 64, 65, 66, 67, 68, 69] In contrast, adrenalectomy produces no change in blood pressure level in post-DCA hypertension.[44] Removal of the adrenals in essential hypertension has been followed by a fall to normal pressure levels in about one third of the patients on whom this procedure has been performed. In the remainder the effect on the blood pressure has been slight or absent.[70, 71, 72, 73, 74, 75, 76, 77]

Cortisone administration produces little or no effect in post-DCA hypertension,[58] but under some circumstances may increase blood pressure in renal-ligature hypertension.[78] In patients with essential hypertension a slight reduction in pressure has been noted,[79, 80, 81, 82] unless renal disease is obviously present, in which case pressure elevations have been observed.[83] In contrast, administration of desoxycorticosterone tends to increase the blood pressure in all of the experimental syndromes, as well as in essential hypertension itself.[60, 84, 85]

Influence of the Kidney

Neurogenic hypertension can be produced in completely nephrectomized animals.[86] Nevertheless, a renal factor appears to play some rôle in this condition, for denervation of the kidney in otherwise sympathectomized neurogenic hypertensive animals is followed by a marked fall in pressure.[5, 87]

Nephrectomy in renal hypertensive dogs is almost invariably followed by a fall in pressure to normal.[14, 62, 88, 89, 90] In rats in which hypertension has been produced by unilateral perinephritis, removal of the involved kidney is followed by a fall in pressure if performed early in the course of the disease, but hypertension may persist if the procedure is done late.[91, 92, 93] Bilateral

nephrectomy in post-DCA hypertension is followed by a reduction in pressure toward or to normal limits.[44, 94] The effects of bilateral nephrectomy in essential hypertension are for obvious reasons, unknown.

Influence of Electrolytes

Extremely low sodium intakes do not appear to influence renal hypertension in dogs,[95] although some reduction appears to occur in the renal-ligatured rat.[96, 97] The effect of low sodium diets in post-DCA hypertension is to lower mortality rates without influencing the level of blood pressure.[44] In essential hypertension, diets of extremely low sodium content have occasionally resulted in blood pressure reduction. The consensus appears to be that in most patients the blood pressure is not changed, although considerable clinical improvement may be observed.[98, 99, 100]

Conversely, high sodium intakes appear to augment all forms of hypertension in which this effect has been studied.[16, 101, 102, 103, 104, 105, 106]

The influence of potassium provides one point of considerable divergence. Low potassium diets are followed by a fall in renal-ligature hypertension to normal limits,[107] whereas similar diets are completely without effect on the blood pressure in post-DCA hypertensive disease.[44] The influence of potassium deficiency in essential hypertension is incompletely known, although hypopotassemia in cases of dehydration and diabetic acidosis is frequently associated with low blood pressure.

The Nervous System

Central nervous system depression, as in sleep or in barbiturate anesthesia, is followed by reduction of the blood pressure in neurogenic hypertension toward normal.[108] In contrast, the pressure in renal hypertension is affected little if any until a late phase of the disease is reached.[109, 110] In post-DCA and in essential hypertension the effects are variable and transient, with some reductions to normal limits.[44, 111]

Somewhat comparable changes follow elimination of the influence of the autonomic nervous system, either through surgical sympathectomy or through the use of ganglionic or adrenergic blocking agents. Total sympathectomy abolishes neurogenic hypertension.[5] In contrast, sympathectomy has no influence on renal hypertension.[112, 113, 114] The effect of sympathectomy in post-DCA hypertension has not been studied. In essential hypertension, as is well known, some patients appear to be benefited while others show little or no response.[115, 116, 117]

The response to blocking agents in neurogenic hypertension is exaggerated.[118] The effect in renal hypertension is a small and variable reduction.[119, 120, 121] Post-DCA hypertension and essential hypertension are similar in that agents such as dibenamine produce variable and transient reductions in both conditions, rarely to normal.[44, 122]

Discussion

The available data indicate that all forms of hypertension involve both nervous and humoral pressor mechanisms to some extent, although neurogenic hypertension is predominantly nervous in origin and renal hypertension predominantly humoral. Both elements are intermixed in post-DCA and essential hypertension to degrees which appear to vary from one animal or human subject to another.

Of all the varieties of experimental hypertension, the post-DCA syndrome most closely resembles the human disease in its functional as well as in its anatomic aspects. It is notable that no other types of hypertension are as independent of the presence of the adrenal cortex for the continued maintenance of elevated blood pressure.

Of potential significance for the treatment of the human patient is the resistance of post-DCA hypertension to all therapeutic efforts, with the sole exception of hypophysectomy. If this experimental disease is analogous to essential hypertension, the intensive study of the hypophysis and related hypothalamic areas becomes of singular importance, as Selye,[123] Heinbecker [124, 125, 126, 127] and Findley [128] have so recently stressed.

Summary

Essential hypertension in man has been compared with experimental neurogenic, renal and post-DCA hypertension as to the influence of the nervous system, the endocrine glands and kidney, and the effects of drugs and electrolyte intake.

The thyroid, parathyroid and gonads appear to have little to do with any of these forms of hypertension. In contrast, the kidney and the hypophysis are involved to some degree in all.

Essential hypertension is simulated most closely, in both its physiologic and anatomic characteristics, by the post-DCA syndrome. Particularly striking is the independence of these two varieties of hypertension of the presence of the adrenal gland.

Results in animals corroborate and emphasize the relative failure of all known methods of clinical therapy. The experimental evidence points to the hypophysis and hypothalamus as perhaps the most promising areas for future investigations of essential hypertension.

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CASE REPORTS

TRACTION DIVERTICULUM OF ESOPHAGUS WITH EXSANGUINATION: REPORT OF A CASE *

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The existence of traction diverticula of the esophagus was described by Rokitansky [1] in 1840. Their association with pulmonary tuberculosis was known to subsequent investigators, particularly Kragh,[2] who in 1921 refuted the theory of congenital origin. These diverticula have generally been regarded as of little clinical importance, despite occasional reports to the contrary. In the following case, fatal exsanguination occurred from a traction diverticulum.

Case Report

In 1942, 10 years prior to his last admission, a 41 year old foundry worker was admitted to this hospital because of shortness of breath and swelling of the legs. He was found to have slight cardiac enlargement, electrocardiographic left axis deviation, and roentgenographic findings of diffuse miliary mottling consistent with silicosis throughout both lung fields, with increased size of lung roots. Blood pressure was 170/110 mm. of Hg. He responded well to diuretics, bed-rest and a short period of digitalization.

He was admitted for the second time in 1944, two years later, because of severe headaches and dizziness. Blood pressure was 212/130 mm. of Hg. Physical examination and chest x-rays were unchanged from his previous admission, and he was discharged after a short period of supportive treatment.

Gastrointestinal bleeding occurred for the first time in 1948, when he vomited some blood-streaked material and subsequently had tarry stools. In 1950 he had a second episode of hematemesis and tarry stools, preceded by a persistent dry cough and two days of blood-streaked sputum. He was admitted to a local hospital, where acid-fast bacilli were found in the sputum, following which he was transferred to this hospital. Past history was noncontributory, except for 20 years of work in a foundry and considerable alcohol intake. There was no history of tuberculosis in his immediate family.

On physical examination the patient was pale and chronically ill, and showed evidence of recent weight loss. Blood pressure was 120/90 mm. of Hg; pulse, 80; respirations, 22; temperature, 97.4° F. Retinoscopy showed marked proliferative retinopathy, with scattered areas of exudate. The heart was questionably enlarged and sounds were of fair quality. A systolic murmur was present over the aortic area.

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The right upper lobe was dull to percussion, with bronchial breath sounds over this area. There was basilar dullness, with poor diaphragmatic motion on the right. The liver was down three fingerbreadths below the right costal margin and had a smooth, soft edge. The rest of the physical examination was essentially negative.

Hemoglobin was 10 gm. per cent; red cell count, 3,170,000; white cell count, 10,100, with normal differential. Bleeding and clotting times were normal. Urine had a specific gravity of 1.008 and contained 1 plus albumin. Nonprotein nitrogen was 48 mg. per cent; fasting blood sugar, 177 mg. per cent; icteric index, 5; brom-

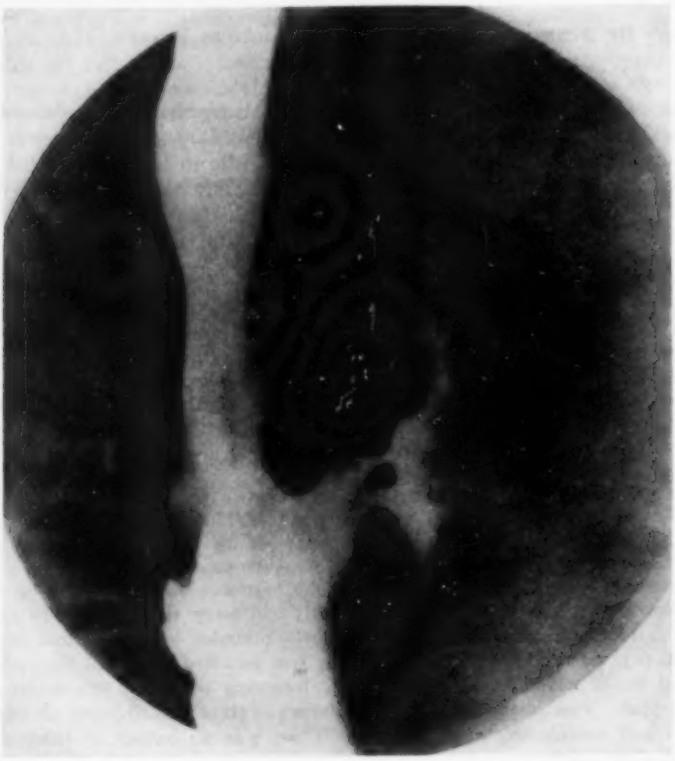

FIG. 1. Traction diverticulum of esophagus, demonstrated by roentgenogram of barium swallow.

sulfalein retention, 24 per cent; cephalin flocculation, negative; prothrombin time, 46 per cent of normal. Acid-fast bacilli were present in smears of sputum. Stools were strongly positive for occult blood. Admission chest x-ray examination showed diffuse nodulations in both lung fields, with superimposed soft infiltrations in both apices, particularly on the right, and retraction of the trachea to the right.

Within hours after admission the patient had a large, tarry bowel movement, following which peripheral circulatory collapse occurred. He responded to intravenous fluids and blood transfusions and was placed on a continuous thrombin regimen via Levine tube. Two days after admission he was started on streptomycin and

para-aminosalicylic acid. Bleeding had stopped by the fourth day and a gastrointestinal series was performed. It revealed a fistulous tract in the esophagus, starting about 3 cm. below the carina, extending anteriorly and branching into two smaller tracts, of which the longer measured about 6 cm. (figure 1). An ovoid deformity was present in the esophagus just above the branching of the fistula. No esophageal varices were found. Examination of the stomach and duodenum was unsatisfactory. On the eleventh hospital day gastrointestinal bleeding began again, with massive melena. A well formed, dark, cylindrical clot was vomited on one occasion. Despite vigorous transfusion therapy the patient went into shock which lasted a week. Finally coma occurred, followed two days later by death.

Postmortem examination showed bilateral pulmonary silicotuberculosis, with markedly enlarged and firm mediastinal and hilar lymph nodes; microscopically, they were fibrotic and hyalinized (figure 2). The esophagus contained numerous small

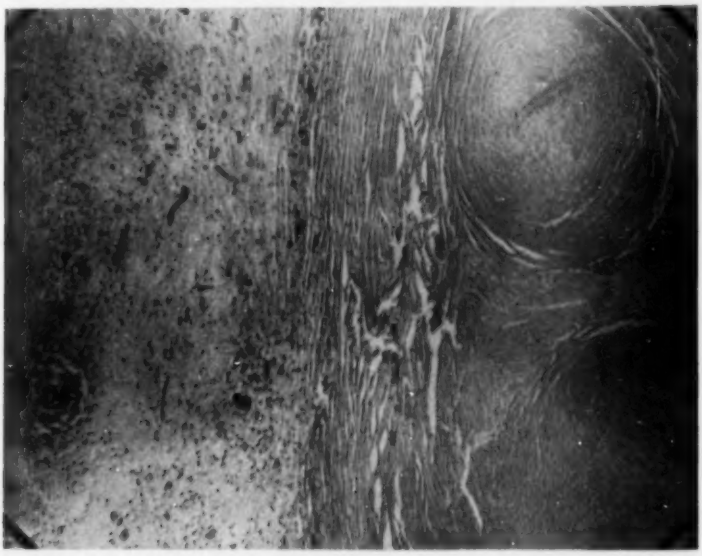

FIG. 2. Low power photomicrograph of silicotuberculous lymph node in bed of esophageal diverticulum.

diverticula. At about the level of the bifurcation of the trachea there was a large diverticulum measuring 3 to 4 mm. across the base. It extended about 5 cm. into the mediastinum and contained a small red blood clot. The diverticulum did not enter the tracheobronchial tree. It was lined by acutely inflamed and congested granulation tissue (figure 3). A giant cell containing a foreign body was present just beneath the capsule, but there was no granuloma formation to indicate tuberculous involvement. A clot consisting of red blood cells and fibrin lay free within the lumen (figure 4). The lower gastrointestinal tract contained much blood within the lumen. There were no other demonstrable bleeding sites. The heart was moderately hypertrophied, weighing 410 gm. The right kidney was very large and finely scarred; it weighed 350 gm. and showed microscopic evidence of arteriolar nephrosclerosis. The left kidney was small, with cortical agenesia.

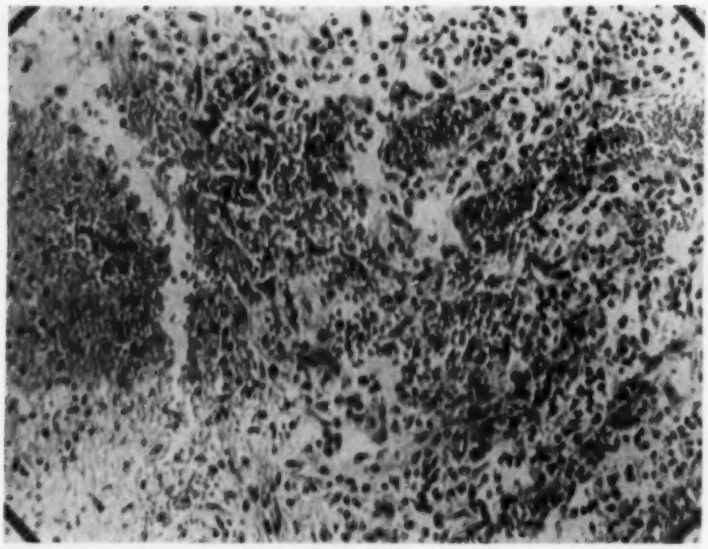

FIG. 3. High dry photomicrograph of wall of esophageal diverticulum, showing granulation tissue and hemorrhage.

FIG. 4. Low power photomicrograph of esophageal diverticulum, showing blood clot in the lumen.

Comment

Traction diverticula of the esophagus have been reported by Kragh [2] and others to occur in 6 to 10 per cent of all cases at postmortem examination. Most of these are seen in patients who have had pulmonary tuberculosis with mediastinal node enlargement, and one report [4] states that 73 per cent of these diverticula show histologic evidence of tuberculosis. They are not often diagnosed clinically because most of them cause no symptoms, but serious complications have been described in the literature. In about 7 per cent of all cases, enlargement of these diverticula may occur [5] and may convert them into the traction-pulsion type, with accumulation of food, feeling of substernal fullness and, occasionally, ulceration. The most frequent complication is perforation, with establishment of an esophagobronchial fistula.[6, 7] Mediastinitis and gangrene of the lung may follow. One author [8] states that 5 per cent of all esophagobronchotracheal fistulae arise from traction diverticula. Gastrointestinal hemorrhage is a rare complication. Three cases have been found in the literature in which major gastrointestinal bleeding occurred.[9, 10] One of these was reported to have had a hematemesis of about 500 c.c. of blood. The case above is the first one reported in which chronic and fatal hemorrhage was a complication of a traction diverticulum of the esophagus.

Summary

A case is reported of a traction diverticulum of the esophagus, complicated by diverticulitis and fatal hemorrhage.

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CRYOGLOBULINEMIA: REPORT OF A CASE ASSOCIATED WITH GANGRENE OF THE DIGITS *

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IN 1947 Lerner and Watson [1] suggested the term "cryoglobulinemia" to describe the presence of a cold precipitable protein in the serum. Three years later Barr, Reader and Wheeler [2] reviewed the literature and found eight cases in which significant amounts of cryoglobulin had been observed; to these they added two of their own. Three additional cases have recently been recorded.[3, 4, 5]

In the case reported here, cold precipitable globulins were demonstrated in association with Raynaud's phenomena which progressed to gangrene and required multiple amputations. To our knowledge this is the first instance in which gangrene has been associated with cryoglobulinemia.

CASE REPORT

A 65 year old married painter was admitted to the Washington University Medical Service of St. Louis City Hospital on September 12, 1949, because of pain in the toes and fingers on exposure to cold. He had experienced similar symptoms during cold weather eight months previously. This pain was described as "burning," and was associated with bluish discoloration and coldness of several toes. No trophic changes were noted. The patient had noticed increasing deafness for 10 years. For several years he had experienced dysuria and nocturia.

He had had gonorrhea at age 20 and a penile sore at age 25, but had not sought treatment for either. The family history was noncontributory. He did not smoke, use excessive amounts of alcohol or take drugs.

Physical examination revealed a well developed, slightly obese elderly white man who was somewhat obtunded and appeared acutely and seriously ill. The temperature was 101.2° F.; pulse, 104/min.; respirations, 24/min.; blood pressure, 210/130 mm. of Hg. The skin was cool and somewhat clammy, with generalized mottled cyanosis. Examination of the eyegrounds revealed only slight arteriolar narrowing and minimal A-V nicking. The heart and lungs were normal. The liver was palpated 5 cm. below the right costal margin in the midclavicular line and was firm, smooth and nontender. The prostate was twice normal size. The right hand was cooler than the forearm and had a bluish mottled appearance. There was dry gangrene of the terminal phalanx of the fifth finger of the left hand. The second and fourth fingers of the left hand and the right great toe were cold and cyanotic. The other toes were also cyanotic but slightly warmer. Brachial, radial, dorsalis pedis and posterior tibial pulsations were of good quality bilaterally. There were moderate varicosities of both legs, and a shallow 2 cm. ulcer was present over the left lateral malleolus. The neurologic examination was normal except for the clouded mental state.

Laboratory findings were as follows: Urinalysis: specific gravity, 1.016; pH, 7.5; sugar, negative; albumin, negative; sediment, rare granular cast. Blood count: red cells, 3,590,000; hemoglobin, 12 gm.; white cells, 14,000; differential count: basophils, 2 per cent; myelocytes, 1 per cent; juvenile forms, 20 per cent; stab forms,

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FIG. 1. Photograph showing the hands after amputations on the first and third admissions.

FIG. 2. Photograph of the ankles and feet showing the mottled cyanosis and amputation sites of the halluces.

25 per cent; segmented forms, 26 per cent; lymphocytes, 22 per cent; monocytes, 4 per cent. Blood Kahn test: negative. Blood chemistry: blood urea nitrogen, 14 mg. per cent; total proteins, 6.9 gm. per cent; albumin, 4 gm. per cent; globulin, 2.9 gm. per cent; cholesterol, 127 mg. per cent; fasting blood sugar, 80 mg. per cent. Blood cultures: negative. Heterophil agglutination: negative. Bleeding time: 2 minutes. Clotting time: 4 minutes. Heparin tolerance test: normal. X-rays of the hands and feet revealed hypertrophic changes around the joints, with moderate osteoporosis of the phalangeal and carpal bones. Calcification of the vessels of the wrist and of the dorsalis pedis arteries was seen. The chest x-ray film was normal. An electrocardiogram revealed delayed atrioventricular conduction (PR interval, 0.24 second). Spinal fluid examination was negative.

Peripheral vascular studies, including temperature and oscillometric readings with nerve block, revealed an adequate blood supply except in the terminal phalanges.

Therapy consisted of Priscoline (2-benzylimidazoline), Etamon (tetraethylammonium chloride), heparin, Dicumarol (bishydroxycoumarin), papaverine and penicillin. The patient remained febrile (100° to 101.2° F.) for five days, after which his temperature returned to normal. The peripheral cyanosis and coldness gradually cleared over a period of 10 days. It was necessary, however, to amputate the left third and fifth fingers and both great toes because of dry gangrene (figures 1 and 2).

A biopsy of skin and muscle was reported as normal. The pathologic report on the digits removed at operation revealed intimal sclerosis and canalized thrombi in the digital arteries (figures 3 and 4).

The patient felt well after the first week in the hospital, his amputation sites healed rapidly, and he was discharged on December 12.

Following discharge the patient had apparently been well except for occasional pains in his hands and feet, especially on exposure to cold. One week prior to admission he developed aching pain in his feet and calves which became progressively worse, and he was readmitted on March 6, 1950.

Physical examination revealed marked cyanosis of the distal 1.5 cm. of the left third finger, and 1 plus edema of the feet and lower legs, with a mottled cyanosis of the overlying skin. Brachial, radial, dorsalis pedis and posterior tibial pulsations were again of good quality. The remainder of the physical examination was unchanged.

The routine blood counts were within normal limits. Total serum proteins, 6.9 gm. per cent; albumin, 3.7 gm. per cent; globulin, 3.2 gm. per cent.

The patient was treated with bed-rest, elevation of the legs and penicillin, with slow but progressive improvement. Peripheral vascular studies again revealed no evidence of occlusive arterial disease. He was discharged much improved on April 8, 1950.

On the day after discharge from the hospital the patient was exposed to cold and developed severe "shooting" pains in the hands. The remaining fingers of the left hand became blue. He was admitted for the third time on April 11, 1950.

Examination revealed mild generalized cyanosis of the right hand. The fingers and stumps of the left hand were markedly cyanotic and cool. There was 1 plus pretibial edema.

The blood counts were again within normal limits. Bence-Jones protein was not demonstrable in the urine. In an attempt to demonstrate cryoglobulins the patient's blood and plasma were cooled slowly to 0° C., but no precipitation could be seen grossly. The bone marrow revealed 15 per cent plasma cells, many with multiple nuclei. These were thought to represent a nonspecific response and were not considered diagnostic of multiple myeloma. Blood chemistry: total proteins, 7.5 gm. per cent; albumin, 3.6 gm. per cent; globulin, 3.9 gm. per cent; calcium, 9.6 mg. per cent; phosphorus, 3.5 mg. per cent; alkaline phosphatase, 1.8 B.U.; bromsulfalein dye retention, 4 per cent in 45 minutes; cephalin-cholesterol flocculation test,

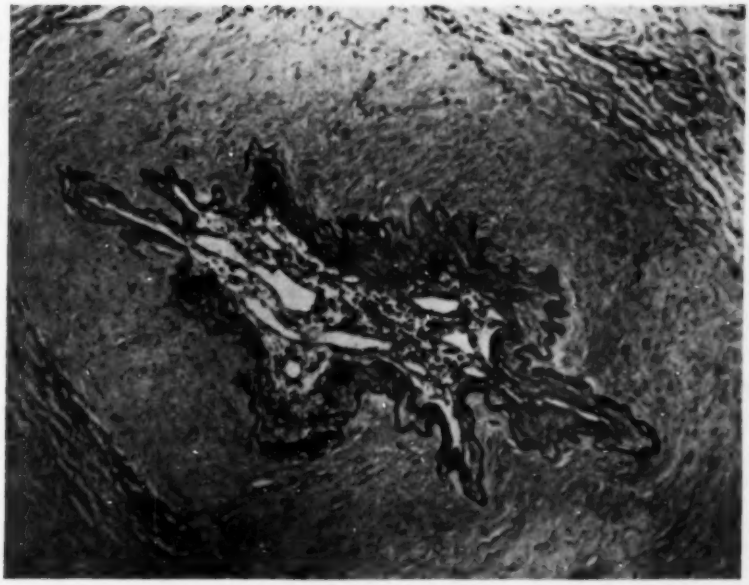

FIG. 3. Photomicrograph (× 100) of a section of a digital artery stained for elastic tissue. The lumen is seen to contain a completely organized and canalized thrombus.

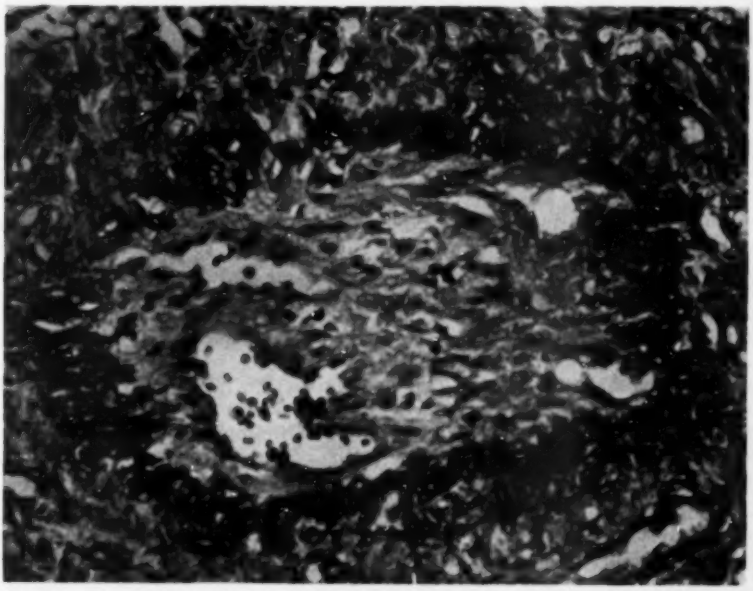

FIG. 4. Photomicrograph (× 400) showing lumen of a branch of a digital artery stained for elastic tissue. The lumen is filled with connective tissue in which are several capillaries.

negative; thymol turbidity, 1 unit; cholesterol, 136 mg. per cent; prothrombin time, 80 per cent of normal. X-ray examination of the skull, pelvis and long bones showed evidence of hypertrophic arthritis.

The patient was again treated with Dicumarol and Priscoline. Although general improvement occurred, the left index finger became gangrenous and was amputated. The patient was discharged on June 18, 1950.

He was asymptomatic for eight months, but following a walk in the cold weather his feet became numb, then painful and slightly swollen. He entered the hospital for the fourth time on February 2, 1951.

On examination the extremities were noted to be cool, with blotchy cyanosis. Brachial, radial, posterior tibial and dorsalis pedis artery pulsations were of good quality.

Routine laboratory studies were essentially unchanged from those noted on previous admissions. Bone marrow examination revealed a cellular marrow with 7.5 per cent plasma cells, many of which were in amitotic division.

There was improvement on therapy consisting of penicillin, Priscoline and papaverine. The patient was discharged on March 11, 1951.

He was admitted for the fifth time on April 13, 1951, in a semicomatose condition. The history, as obtained from relatives, revealed that he had been well until the day of admission, when suddenly he became drowsy and rapidly progressed to a state of unconsciousness.

At the time of the physical examination the patient was semicomatose. The rectal temperature was 96° F.; pulse, 80/minute; respirations, 18/minute; blood pressure, 120/60 mm. of Hg. There was slight cyanosis of the face. Examination of the eyegrounds revealed only moderate arteriolar narrowing with slight A-V nicking. The neck was supple. Respirations were labored and stertorous, but examination of the heart and lungs revealed no abnormal physical findings. There was mottled cyanosis of the skin of the legs, and the hands and feet were cool. Deep tendon reflexes were active and equal, and no neurologic abnormalities could be elicited.

The laboratory data were as follows: Urinalysis: specific gravity, 1.009; pH, 4.5; albumin, 1 plus; sugar, negative; acetone, negative; Bence-Jones protein, negative; sediment, occasional white blood cell per high power field. Blood count: red cells, 4,970,000; white cells, 11,000; hemoglobin, 13.5 gm.; differential count: basophils, 1 per cent; eosinophils, 2 per cent; stab forms, 6 per cent; segmented forms, 48 per cent; lymphocytes, 33 per cent; monocytes, 10 per cent; platelets, 755,000; reticulocytes, 1.7 per cent. Stool: guaiac negative. Blood sugar, calcium, phosphorus, bromsulfalein retention, alkaline phosphatase, cephalin-cholesterol flocculation, thymol turbidity, total and fractional proteins, and cholesterol determinations were within normal limits. Supravital preparations of the peripheral blood, when cooled to 6° C., revealed pink-staining inclusions within the monocytes and neutrophils. Whole blood or plasma, when cooled in ice water, was noted to gel, the gel disappearing when the blood was rewarmed. The patient's serum, when added to normal blood and cooled, resulted in the appearance of inclusion bodies in the neutrophils. Examination of the bone marrow (supravital stain) revealed normal myeloid elements and slight erythroid stimulation. There were 6.5 per cent plasma cells. Pink-staining inclusions were noted in the segmented neutrophils and the stab forms. Quantitative studies on cooled serum revealed 1.6 gm. per cent of cryoglobulin.* Repeat x-rays of the skull and long bones revealed osteoporosis only.

* The cryoglobulins were measured in the following manner: Protein fractionation was done on the serum at room temperature. A second portion of the serum was chilled at 6° C. overnight and then spun for 30 minutes at high speed in a refrigerated centrifuge. The supernatant serum was then separated from the precipitated protein and a second protein fractionation was done. The difference in the two globulin values was assumed to be cryoglobulin which had been precipitated by cold.

Therapy consisted of nasal oxygen, parenteral fluids and penicillin. Within 24 hours the patient regained consciousness and was able to move his extremities. His sensorium became clear and the hospital course was uneventful thereafter. The hands, lower legs and feet, however, continued to be cool and to exhibit a mottled cyanosis. The patient was discharged on June 9, 1951.

On November 10 he entered the hospital for the sixth time because of numbness and burning pain in the hands and feet. Five days prior to admission, during exposure to cold, he had noted the return of numbness, coldness and tingling of the feet and hands. He returned to the hospital so that he could remain in a warm environment.

Physical examination was essentially the same as on previous admissions. Blood pressure was 120/80 mm. of Hg. There was no cyanosis or gangrene noted. There were good pulsations of the peripheral arteries.

Laboratory data, including urinalysis, complete blood counts, serum proteins and alkaline phosphatase, showed no significant changes. Bone marrow examination again revealed an increase in plasma cells (8 per cent).

The patient had been well for 15 months when his hands and feet again became painful and numb following exposure to cold. He entered the hospital for the seventh time on March 17, 1953.

Examination revealed a mottled cyanosis of both hands and feet, with gangrene of the right fifth finger. The blood pressure was 160/100 mm. of Hg. The remainder of the physical examination was unchanged.

The laboratory data were as follows: Urinalysis: specific gravity, 1.010; albumin, negative; sugar, negative; Bence-Jones protein, negative; sediment, occasional white blood cell per high power field. Blood count: red cells, 4,500,000; white cells, 11,000; hemoglobin, 14 gm.; differential count: basophils, 1 per cent; stab forms, 6 per cent; segmented forms, 68 per cent; lymphocytes, 23 per cent; monocytes, 2 per cent. Cephalin-cholesterol flocculation, thymol turbidity, blood calcium and blood phosphorus determinations were within normal limits. Total proteins, 7.5 gm. per cent; albumin, 3.2 gm. per cent; globulin, 4.30 gm. per cent. Quantitative studies on cooled serum revealed 1.8 gm. per cent of cryoglobulin. X-ray examination of the skull, pelvis and long bones revealed no changes from previous studies. No lupus erythematosus cells could be demonstrated.

It was necessary to amputate the right fifth finger because of dry gangrene. Later, the distal phalanges of the left thumb and left fourth finger became gangrenous and were amputated.

Discussion

The patient who is the subject of this paper had seven hospital admissions, six of which were for symptoms precipitated by exposure to cold. The major manifestation was that of severe Raynaud's phenomenon, which progressed to gangrene and necessitated amputation of eight digits. Raynaud's phenomena of a milder degree, induced by exposure to cold, were present in six of the 10 cases of cryoglobulinemia reported by Barr.[2]

The histologic sections of the amputated digits revealed moderate hyperplastic arteriosclerosis with organized thrombi and recanalization. The organization of the thrombi was so advanced that the latter must have antedated by several months the onset of gangrene. These old occlusions could have arisen on the basis of cryoglobulins, since the patient's symptoms of ischemia had been precipitated by exposure to cold several months previously. Thrombosis of the retinal vessels has been observed,[2] and intravascular gelatinous material has been demonstrated post mortem.[2, 6] It seems reasonable to assume that the precipitation of cold sensitive globulins in the presence of diminished vascular reserve was

responsible for the occurrence of gangrene. Other causes for the gangrene seem unlikely. According to Allen, Barker and Hines,[7] such extensive gangrene does not occur in Raynaud's disease. The lesions as observed microscopically in this case were not compatible with thromboangiitis obliterans; calcification of vessels by x-ray constitutes additional evidence against this diagnosis. Normal oscillometric studies, the reversibility of the cyanosis, and involvement of the upper extremities would indicate that obliterative arteriosclerosis was not of primary etiologic significance.

A definitive primary diagnosis cannot be made in this case. It is suggestive of multiple myeloma, but several sternal marrow studies revealed no myeloma cells; the increase in plasma cells is not of itself diagnostic of this disease. It would be unusual in multiple myeloma not to find significant involvement of the skeletal system four years after the onset of the symptoms. Even though amputation of several digits has been necessary, our patient is only moderately disabled. None of the other diseases which have been associated with cryoglobulinemia seems likely in our patient.

Multiple myeloma was the primary diagnosis in six of the 10 cases of cryoglobulinemia reviewed by Barr.[2] However, his study of 121 cases of hyperglobulinemia revealed only one case of multiple myeloma with a cold precipitable protein, and then only a trace was found. Bayrd and Heck,[8] in an analysis of 83 cases of multiple myeloma, do not report the occurrence of cryoglobulins. It is apparent, however, that cryoglobulins may easily escape detection if not searched for specifically. Most and Lavietes[9] observed cold precipitable proteins in many active cases of kala-azar. Barr et al.[2] found cryoglobulins (approximately 22 mg. per cent) in Raynaud's syndrome, disseminated lupus erythematosus, Buerger's disease, lymphogranuloma venereum and liver disease. Cryoglobulins ("in amounts greater than 10 mg. per cent") have been found in bronchiectasis, rheumatic fever, bacterial endocarditis and lymphatic leukemia by Lerner, Barnum and Watson.[10] Traces of cryoglobulins have been found in many miscellaneous diseases.[2, 10]

The clinical manifestations attributed to cold-precipitable globulins are purpura, Raynaud's syndrome, deafness, mottling of the extremities, bleeding from the nose and gums and extensive retinal hemorrhages.[1] The manifestations in the present case, for which cryoglobulins were probably responsible, were sensitivity to cold, deafness and blotchy cyanosis.

One of our patient's hospital admissions was for sudden loss of consciousness. Cryoglobulins (1.6 gm. per cent) were demonstrated at this time. The patient remained semicomatose for 24 hours, gradually regained consciousness, and demonstrated no neurologic sequelae. Whether the patient's severe (but reversible) neurologic disorder was related to the presence of cryoglobulins in his blood must remain a matter of speculation. However, Barr et al.[2] have described a slowing of the circulation in the conjunctival vessels and actual sludging of blood after the application of cold. In none of the reported cases of cryoglobulinemia has there been evidence of impairment of cerebral circulation.

The relationship of cold agglutinins to cryoglobulins is not clear. However, autohemagglutination, acrocyanosis and Raynaud's phenomena were present in a patient whose serum contained cold agglutinins.[11] Cold agglutinins were not demonstrated in our patient's serum.

SUMMARY

A case is reported of cryoglobulinemia manifested by severe Raynaud's disease which progressed to gangrene and required multiple amputations. To our knowledge, this is the first instance reported in which gangrene has been associated with cryoglobulinemia.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Dr. Charles Sprague for the hematologic and special protein fractionation studies; to Dr. John Bauer for the photomicrographs, and to Dr. John Saxton, of the Snodgras Laboratory of St. Louis City Hospital, for pathologic reports and chemical determinations.

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A CASE OF HYPERPARATHYROIDISM WITH UNUSUAL DEFORMITY OF THE THORACIC CAGE*

By HAROLD O. SCHNEIDER, M.D., *Salem, Oregon*

HYPERPARATHYROIDISM is now a well established and adequately described condition, but some of its more unusual manifestations are not so well recognized. A recently observed case presented a profound deformity of the thoracic

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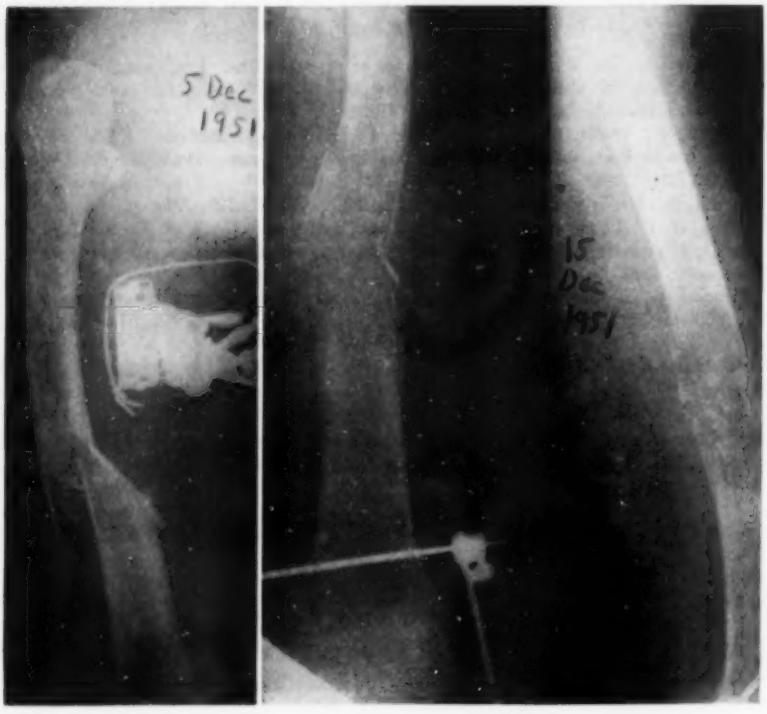
cage, marked clubbing of the fingers, a large mass in the thyroid area which proved to be a cystic parathyroid adenoma, and an extraordinarily high serum calcium (29.0 mg. per cent). These features seemed uncommon enough to warrant reporting the case. The smooth postoperative course of the patient in the face of the exceedingly high serum calcium and large parathyroid tumor is also of interest.

Case Report

A 58 year old man was admitted to the hospital December 5, 1951, with a fracture of the right femur incurred by the insignificant trauma of tripping on a rug.



A *B*

Fig. 1 *A*. Admission. *B*. Tenth day.

He had had no previous fractures. The affected extremity was placed in traction and after one week in bed he began to have persistent vomiting and weakness. Because of this and the findings on x-ray examination, consultation with the author was requested (figure 1 *A* and *B*).

The patient's history was obtained with difficulty because of his extreme weakness and impaired hearing. His voice was barely audible. With the assistance of his family it was learned that his weakness had begun five years previously and had recently become extreme. Previous examinations had repeatedly failed to disclose

an adequate cause for his complaints. He was known to have had a large mass in his neck for several years, presumed to be a simple colloid goiter. The patient was aware that the mass had increased somewhat in size in the last two months. Anemia of unexplained cause had also been previously disclosed.

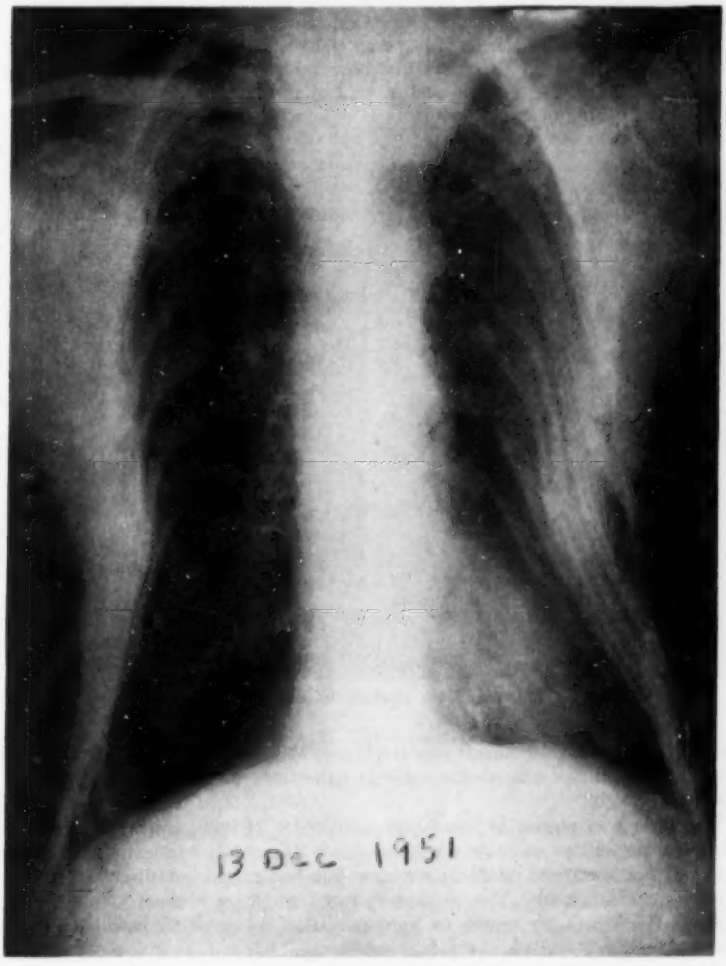


FIG. 2. Thoracic cage. Preoperative chest x-ray. Note rib deformity.

For the last three years the patient's appetite had gradually diminished but he had been unduly thirsty, usually drinking two quarts of carbonated beverage in the evening. He was not a milk drinker. Frequency and nocturia troubled him but he was without prior digestive complaints. His teeth had become loose five years

before and "fell out in a matter of a few months." (No epulis was present, at least from description and further questioning.) His lack of muscular strength, frequent muscular cramps, aching in "every bone of the body," loss of stature from five feet six inches to five feet three inches, and progressive stooping of his shoulders convinced him that he had become a prematurely old man. In the preceding six months he had lost 15 pounds, so that he weighed an estimated 100 pounds upon admission to the hospital.

He was extremely undernourished and pale, and constantly moistened his lips and tongue with ice water to satisfy his thirst. He had no fever. The blood pressure was 120 mm. of Hg systolic and 80 mm. diastolic. The pulse rate was 76 per minute, regular and of good volume. His general weakness and voice changes were striking, as was his marked generalized muscular hypotony.

His mouth was edentulous. Examination of his eyes failed to disclose the band-shaped keratitis occasionally present in this condition. A soft mass present in the neck had the appearance of an ordinary thyroid enlargement and measured ap-

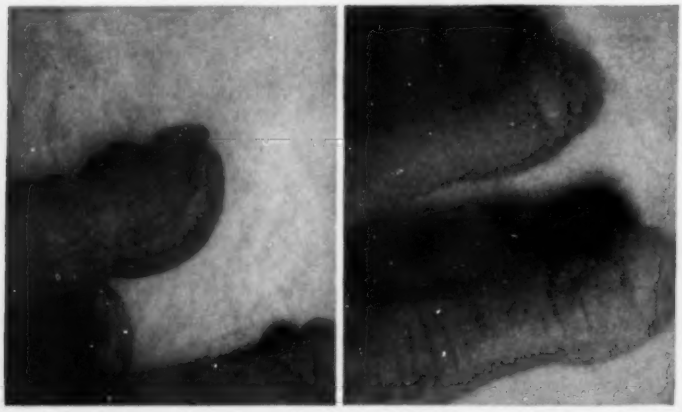


FIG. 3. Clubbing of the fingers. Note marked deformity of the nails on the lateral view.

proximately 12 cm. by 10 cm.; it was freely movable and nontender, and had a cystic character. The tumor extended equally to either side of the midline just above the suprasternal notch.

His chest was pigeon breasted and exhibited a striking concavity in its lateral dimensions, as well as extreme dorsal kyphosis (figure 2). Breathing was difficult because of his weakened thoracic muscles, but he seemed to suffer no serious respiratory embarrassment. The respiratory rate was 18 per minute. No cyanosis was detected. His ribs were tender to light palpation, as were the small bones of the hands and feet.

Pronounced clubbing of his fingers (figure 3) gave his hands a remarkable appearance. On the dorsum of the third metacarpal bone of his left hand was a cystic, globular lesion measuring 3 cm. in diameter. This is well demonstrated on the x-ray view of his hands (figure 4 *A* and *B*). His tendon reflexes were barely obtainable. The only other abnormal physical finding was the presence of the fractured femur held in traction.

Table 1 lists the laboratory studies performed. The serum calcium level of 29.0 mg. per cent was found on two occasions and was confirmed in two separate laboratories in each instance.

The patient was immediately placed on a low calcium-low phosphorus diet containing 0.137 gm. of calcium, which closely approximated the constituents recommended by Albright.[1] No prior fluid balance record was available when this was first instituted. He was found while under treatment to have a 24 hour intake of 940 c.c. orally and a 1,600 c.c. urinary output. Parenteral fluids in the form of 5 per cent dextrose in saline were administered.

A *B*

FIG. 4 *A* and *B*. X-rays of left hand. The roentgenogram well demonstrates the cystic lesion of the third metacarpal. Note progress of healing demonstrated in *B* on the seventy-eighth day.

After the diagnosis of hyperparathyroidism was established the patient was treated as a surgical emergency and the parathyroid tumor described above was removed. The immediate postoperative course was satisfactory. Contrary to expectation, even though widespread bone disease was present he did not manifest postoperative tetany. His blood serum calcium concentration rapidly returned to normal and did not go below 8.6 mg. per cent, this on the ninth postoperative day (table 1). Renal function rapidly improved to normal. His urinary output on the first postoperative day was 760 c.c. Within 48 hours he was able to consume a high calcium-low phosphorus diet. Parenteral feeding of calcium was never necessary to feed the "hungry bones."

It is interesting to note that within eight days after operation the calcium and phosphorus blood serum concentrations were normal. The blood urea was slower

in its return to acceptable levels, reaching 16.8 mg. per cent by the thirty-eighth postoperative day (table 1).

The rapid recalcification of his skeleton and prompt healing of his fracture are demonstrated in figure 5 *A* and *B*, taken on the seventy-eighth hospital day.

Pathology Report: Gross Specimen and Microscopic Examination (figure 6): The gross specimen consisted of a collapsed, thin walled cyst. When recon-

TABLE I

LABORATORY DATA

Blood Chemical Data

Date	Calcium	Phosphorus	Proteins	Phosphatase (Bodansky Units)	Chloride	Blood Urea
12–14–51	29	2.1	6.5	13.2	410	66 mg. %
12–15–51			Day of Operation			
12–17–51	13.2	2.1		13.2		44
12–18–51	11.2					
12–19–51	9.1	2.83		14.17		
12–20–51	9.16					
12–24–51	8.6	3.5		16.2		
12–28–51	9.0	3.5		16.2		
12–30–51	9.0	3.8		10		25
1–10–52	9.09	3.8		13		
1–23–52	9.8	3.5		7.8		16.8
2–22–52	9.3	4.0		3.5		15

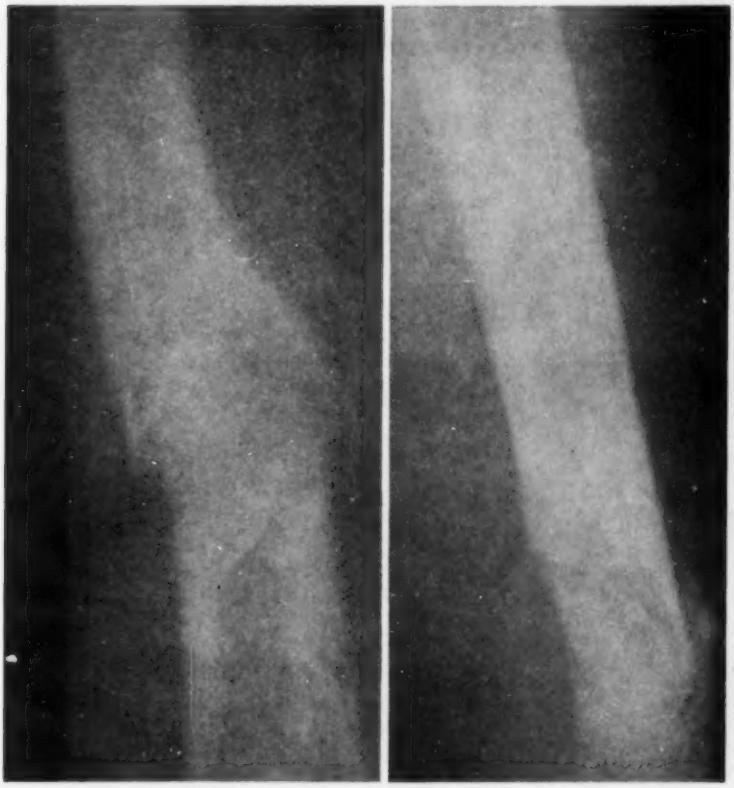
Miscellaneous Laboratory Data

	Blood						Urine						
	RBC	WBC	Hb.	Alb.	Glob.	CO_2 vol. %	Sp. Gr.	pH	Alb.	Sugar	Acetone	Calcium	Micro.
12– 6–51	3,720,000	11,650					1.002	7.0	Neg.	Neg.	Neg.		Neg.
12–14–51				4.1	2.4							Pos.	
12–17–51						45							
12–20–51	3,980,000	6,950	72%, 10 gm.			62						Neg.	
2–22–52	4,540,000	9,700	84%				1.005	6.5	Neg.		Neg.		

structed it measured approximately 5.5. cm. in diameter. It had a slightly abraded outer surface which varied from gray to pink to deep reddish purple in color. The surface was free of adherent thyroid parenchyma or other identifiable tissue. The lumen was opened and the lining completely exposed. When this was done a small amount of soft, brown, easily compressed tissue was detached and appeared to have been lying free within this space. Such tissue undoubtedly was freed from the loosely arranged, softened, plaquelike nodular areas of the lining. Only one such sessile deposit was noted and this had a diameter of 2.2 cm. An immediate frozen section of the detached part was examined. The tissue closely resembled that of

parathyroid gland. The other parts of the wall were of paper thinness and showed no additional distinguishing features.

Microscopic Examination: Several parts of the brown softened and detached portions of the cyst lining were examined. In some areas there were closely arranged cells of round or oval shape which were quite uniform in appearance except for variation in the size of the nuclei. Some of the nuclei had a deep staining,



A *B*

FIG. 5 *A* and *B*. Seventy-eighth day (February 21, 1952) revealing considerable recalcification of pathological fracture. *A*, lateral-mesial aspect; *B*, anterior-posterior aspect.

granular appearance. These cells were arranged in cords, with scanty intervening stroma containing small, blood-filled capillaries. The cytoplasm of these cells was moderately clear in some but in others was granular and pink staining. Their arrangement and general appearance indicated that they were of the principal type. Other cells were arranged in somewhat similar manner but differed in their larger size and more abundant acidophilic cytoplasm. The nuclei of these also appeared

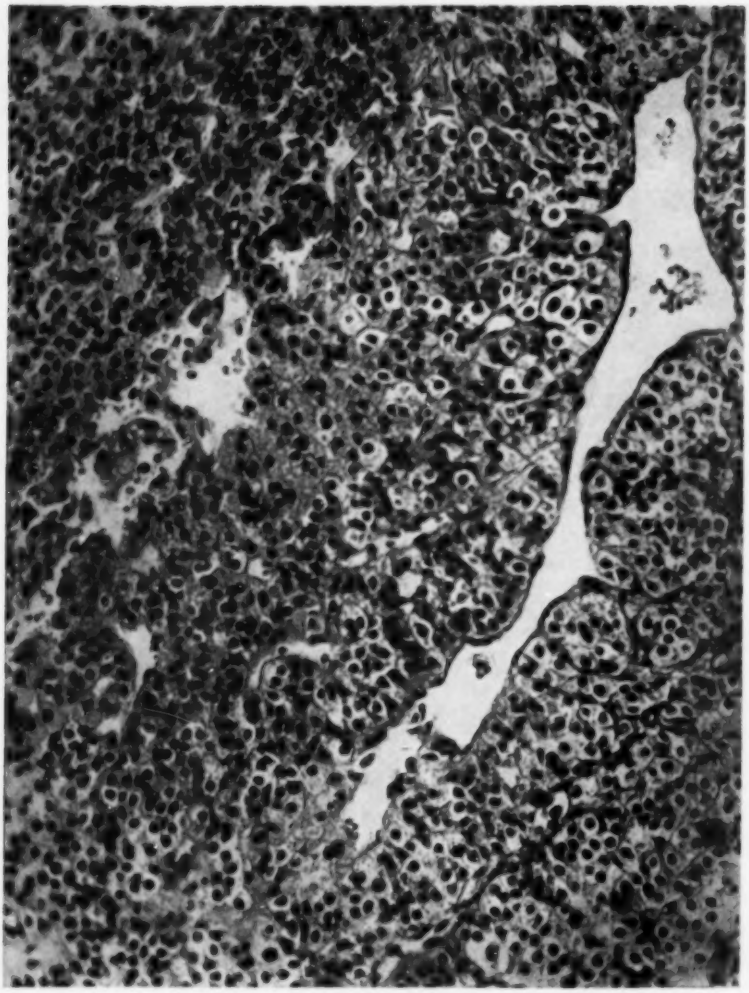


FIG. 6. Microscopic specimen.

round or oval in shape but showed less variation in size than in the cells already described. The staining reaction and the morphology of the latter indicated that they were of the oxyphil type. Pathologic diagnosis: Cystic adenoma of the left inferior parathyroid gland.

DISCUSSION

Hyperparathyroidism is often accompanied by polydipsia and polyuria, sometimes of such severity as to suggest diabetes insipidus. This patient consumed

several gallons of water a day, and his resultant polyuria was associated with the passage of dilute urine. Albright and Reifenstein [1] have demonstrated the loss of both base and chloride under such circumstances. Hypochloremia was observed in this individual. This alteration in physiology is caused by renal tubular damage incurred by the plugging of the collecting tubules with calcium casts.

The hypercalciuria and hyperphosphaturia explain to a large degree the loss of fixed base. The hypochloremia is explained by the loss of chloride through failure of tubular function. This further contributes to the loss of fixed base. The loss of chlorides is enhanced in some measure by vomiting.

FIG. 7. Nephrocalcinosis, right kidney area.

The x-ray appearance of the kidney shadows (figure 7) and the associated azotemia in this case are more in keeping with a diffuse nephrocalcinosis than with renal lithiasis. (Unfortunately the deposition of calcium in this instance is not well reproduced by photography.) Albright and Reinfenstein have stated that nephrocalcinosis may exist without being visible by x-ray. The prompt disappearance of polydipsia and polyuria after removal of the parathyroid tumor and the return of the serum calcium levels to normal are evidence that these symptoms are probably the result of hypercalcemia.

Albright and his associates have observed that alarming oliguria may occur following removal of parathyroid tumors which may be accompanied by fatal renal insufficiency. This turn of events is most frequent when azotemia is present

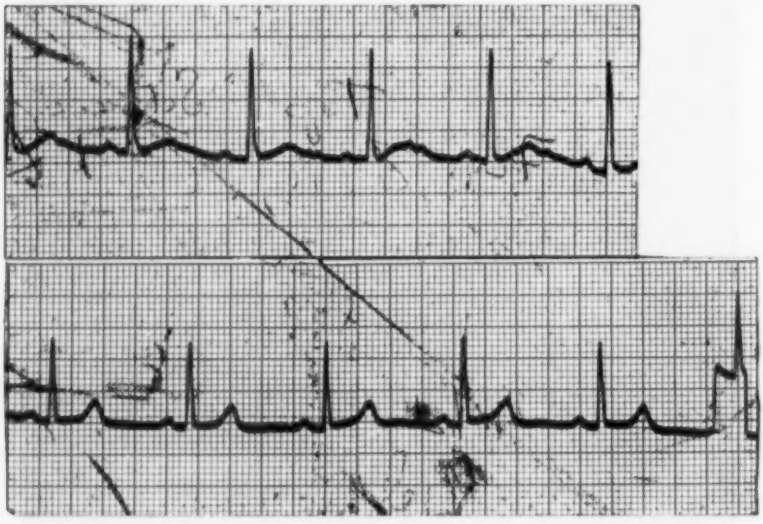


FIG. 8. *Above*, December 15, 1951, Lead II. Rate 80; PR interval, 0.16 sec.; QRS, 0.08 sec.; QT time, 0.28 sec. (normal, 0.34 to 0.37). Note prominent U waves. *Below*, January 29, 1952. Rate 70; PR interval, 0.16 sec.; QRS, 0.04 sec.; QT, 0.36 sec. (normal, 0.36 to 0.39).

prior to surgery. Transient oliguria made its appearance in this patient on the first postoperative day, but gratifying recovery of urinary output followed.

Hypercalcemia is not often the cause of gastrointestinal symptoms, but when it is such symptoms may clearly simulate major gastrointestinal disease. Occasionally digestive tract complaints may occur without the skeletal or renal manifestations of hyperparathyroidism. Intractable duodenal ulcer, resistant to medical management, has been reported.[2, 3] Vomiting, when present, is usually of a pernicious type and may at times be projectile.

It is of particular interest that the gastrointestinal manifestations of this man's illness began with his confinement to bed, since numerous writers have pointed out that with immobilization the normal skeleton, is, at times, rapidly demineral-

ized. This change has been shown to cause hypercalcemia, hypercalciuria and immobilization stones. Such changes are most frequent in youths who have had fractures, and in the case of fractures that occur in individuals who have Paget's disease of bone or early osteoporosis.

How much immobilization contributed to this individual's nausea and vomiting, in view of his already markedly demineralized skeleton, is a matter of conjecture However, his course suggests that bed-rest may have been responsible in some measure for the high level of the blood calcium.

Muscular weakness in hyperparathyroidism is frequent and, when present, is usually accompanied by muscular flaccidity, hyporeflexia and hypermobility of the joints. These features are thought to be the result of hypercalcemia. It is well known that hypocalcemia causes increased excitability of the nerve muscle apparatus, in contrast to decreased excitability in the presence of hypercalcemia. This lack of muscle tone involves smooth muscle as well as skeletal, and serves to explain a number of symptoms due to muscular hypotonicity. Fortunately these changes are reversible.

Alteration in the serum concentration of calcium has been shown to affect the duration of the Q–T interval of the electrocardiogram. In hypercalcemia the Q–T interval is usually short, and the T waves may be flat or reversed. This change is presumed to be due to the increased concentration of ionic calcium in the cardiac perfusion fluid. These electrocardiographic findings, however, are an exceedingly poor index of ionic calcium concentration and have virtually no clinical diagnostic value. This patient's shortened Q–T interval of 0.28 second at a cardiac rate of 80 is of added interest (figure 8). Normal (from Ashman and Hull), 0.374.

Anemia in hyperparathyroidism is not often encountered but, when present, is due to bone marrow fibrosis, depression of kidney function, or alterations of total body nutrition. Outspoken gastrointestinal complications increase this tendency.

Numerous changes in the structure of the bony skeleton can occur in hyperparathyroidism. (The presence of bone disease is dependent upon the degree of negative calcium balance. As noted in this man's history, he was not a milk drinker.) Fractures, bone deformity, giant cell tumors, diffuse osteoporosis or more classic generalized cystic changes have been well documented. This case presents many of the common skeletal features of this disease, including generalized osteitis fibrosa, pathologic fracture and bone deformity. The most outstanding change observed in the skeleton was the marked softening of the ribs, with partial collapse of the thoracic cage. Dyspnea due to this was sufficiently prominent to suggest a resultant secondary reduction in vital capacity.

According to Snapper,[4] clubbing of the fingers is a rather unusual feature of hyperparathyroidism. The author is unaware of any published photographs of this condition showing its close resemblance to hypertrophic pulmonary osteoarthropathy (figure 3). The lateral view of the nails discloses a more concave depression than that usually seen in pulmonary osteoarthropathy. In the latter condition a bulbous enlargement of the terminal phalanges occurs due to proliferation of the soft tissues. The ungual phalanx is often found by x-ray to be enlarged. On the other hand, the changes in the phalanges found in hyperparathyroidism give the appearance of being depressed and everted because of a lack

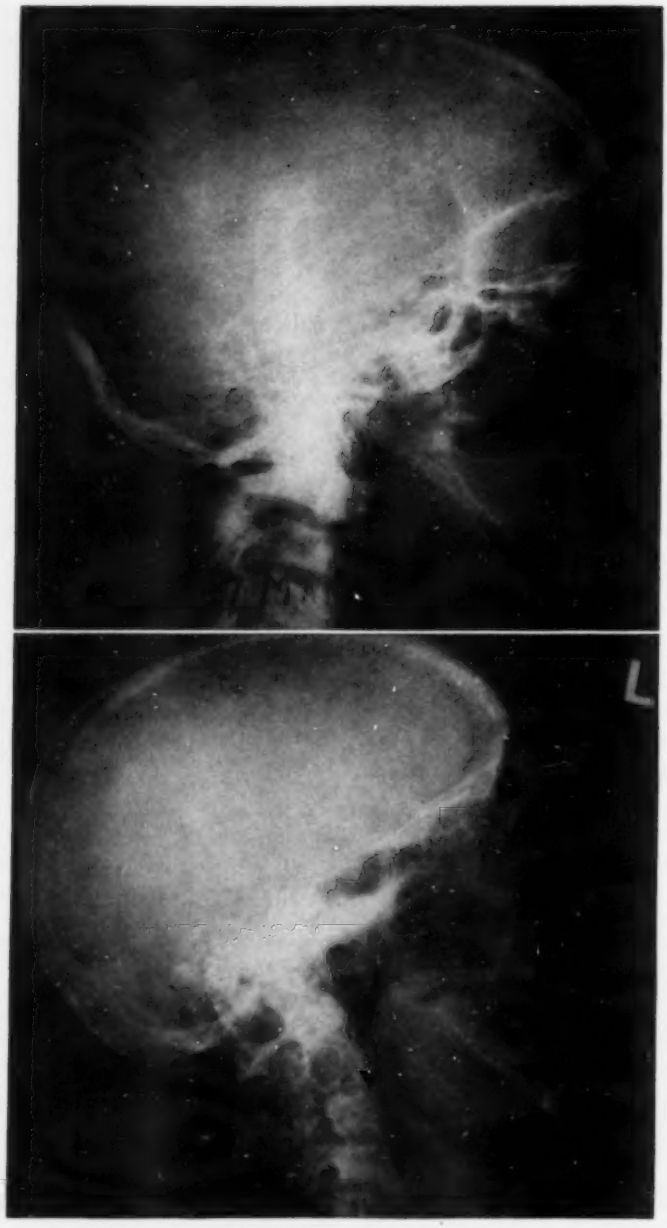


FIG. 9. Skull, left lateral. Although no reference was made to the findings noted in the skull this is added to disclose how much the skull was spared as compared to other areas of the skeleton.

of underlying rigid bony support. This is suggested by the x-ray appearance of the hands (figure 4 *A* and *B*).

SUMMARY

A case of hyperparathyroidism has been presented in which the serum calcium concentration was reported to be 29.0 mg. per cent, one of the highest on record. Several unusual features of this disease are presented, including unusual deformity of the thoracic cage, clubbing of the fingers, and an unusually large cystadenoma of the parathyroid that had the outward appearance of a simple colloid goiter. X-ray examination and photographic plates of some of these changes are presented. Of further interest is the remarkably smooth immediate postoperative recovery of a moribund individual who manifested far advanced complications of this disease. Virtually all of the manifestations of hyperparathyroidism, as described by Albright, occurred in this individual.

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JAUNDICE DUE TO METASTATIC OBSTRUCTIVE LESIONS*

By WILLIAM F. CERNOCK, M.D., *Chicago, Illinois*

JAUNDICE resulting from obstruction of the common bile duct by invasion of the duct or by pressure from enlarged portal nodes is frequently mentioned, but actual reports are rarely found. Textbooks [1-7] mention obstructive lesions associated with leukemia, infectious mononucleosis, lymphosarcoma, Hodgkin's disease, gummas and carcinoma without quoting specific references.

A review of the literature since 1900 disclosed only five reported cases of obstructive jaundice caused by metastatic lesions in the ducts or by compression from enlarged lymph nodes. Herbut and Watson [8] reported three cases, two associated with carcinomas of the colon and one with a lymphosarcoma. Bile duct obstruction, due to leukemic invasion of the portal nodes, is reported in one case by Bower and Coca-Mir.[9] Goldman and Engbring [10] reported a case due to metastases from a carcinoma of the nasopharynx.

* Received for publication March 16, 1953.
From Mercy Hospital and the Department of Medicine, Stritch School of Medicine, Loyola University, Chicago, Illinois.

Case Report

A 42 year old white female who had had a left radical mastectomy for carcinoma of the breast in September, 1949, was admitted to Mercy Hospital on December 11, 1949, because of dyspnea.

Physical examination disclosed bilateral pleural effusions. The liver edge was palpable 2 cm. below the costal margin. No lymph nodes were palpable. There was bilateral ankle edema. Examination of pleural fluid obtained from three different aspirations failed to reveal tumor cells. Shortly after mercurial diuretics were used to relieve the edema the patient developed an exfoliative dermatitis and jaundice. It was felt that she had developed a toxic hepatitis. A liver biopsy disclosed dilated bile ducts consistent with an obstruction rather than with a toxic hepatitis. The jaundice increased and the patient died on January 12, 1950.

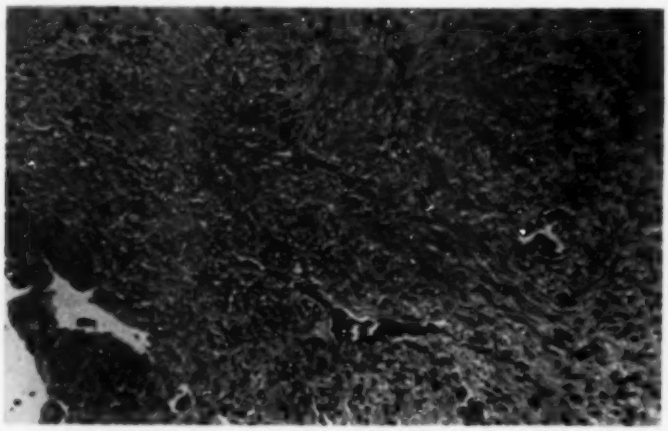

Fig. 1. Infiltration of the common bile duct, at the point of constriction, by metastatic tumor cells. Mucosa at the left lower corner.

At necropsy the liver weighed 1,760 gm. The color was steel-blue mixed with yellow-brown. Scattered over the surface of the left lobe were metastatic nodules which measured up to 7 mm. The gall-bladder was markedly distended and was greenish black in color. It measured 15 cm. in length. The common bile duct was enlarged and was 1 cm. in its greatest diameter. At the point where the common duct was surrounded by the pancreas, there was a constriction due to pressure from a marble-sized lymph node. Sections made through the liver showed areas of cloudy swelling, together with areas of focal necrosis. There was general distention of the biliary ducts throughout the section. Many of the necrotic areas were located about distended biliary ducts. Sections made through the common bile duct at the site of constriction revealed massive infiltration of the wall with irregular hypochromatic tumor cells (figure 1).

Comments

Jaundice due to metastatic lesions usually results from massive destruction of hepatic parenchyma by malignant tissue; however, it may also result from obstruction of the extrahepatic biliary system.

Clinically, this case presented a diagnostic problem. The jaundice was of short duration, and since it followed the administration of a mercurial diuretic and the onset of a generalized exfoliative dermatitis, the first impression was that the patient was suffering from an acute hepatitis as a result of mercurial toxicity. Liver biopsy did not verify the diagnosis of hepatitis but rather suggested that the jaundice was obstructive in nature.

SUMMARY

1. Jaundice due to obstruction of the extrahepatic bile ducts by invasion of the ducts or by enlarged portal lymph nodes is frequently mentioned but seldom seen.

2. A summary of a thorough search of the literature on the subject of jaundice due to metastatic obstructive lesions is presented.

3. A sixth case, with obstruction of the extrahepatic bile ducts due both to invasion of the common bile duct and enlarged lymph nodes produced by metastases from a carcinoma of the left breast, is recorded.

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THROMBOTIC THROMBOCYTOPENIC PURPURA *

By WAVERLY S. GREEN, JR., M.D., *Baltimore, Maryland,* and THOMAS W. GREEN, M.D., *Richlands, Virginia*

THROMBOTIC thrombocytopenic purpura is a rare disease of which only a few cases have been diagnosed ante mortem.[4] Because of the rarity of diagnosis, other than at the autopsy table, few laboratory data pertaining to the interesting

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hematologic features of this disease have been recorded. The literature has been reviewed recently and the clinical features of the syndrome seem well established.[5] We have had the opportunity to study a case of this disease prior to death and were able to perform several tests of interest in the further understanding of this syndrome.

Case Report

A 64 year old white female was admitted to the hospital on January 25, 1952. The family and past histories were noncontributory. Five weeks prior to admission she had fractured the external malleolus of the right ankle, which was then immobilized in a cast. There were no other unusual medical findings at that time. About 10 days prior to entry her family noticed that her speech had become difficult to understand and that she was acting strangely. Three days later she developed nausea and vomiting. Blood appeared in the stools and the urine became dark. Several days later it was noticed that she was jaundiced.

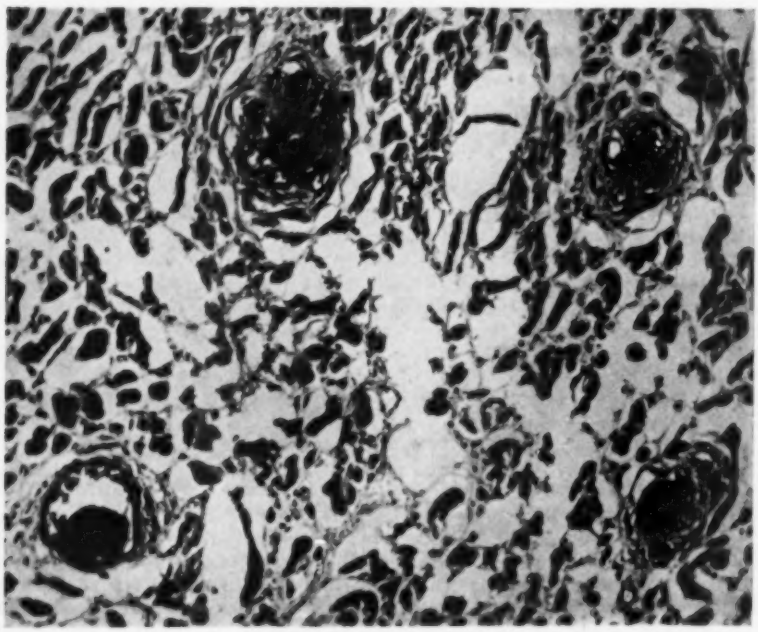

Fig. 1. Heart muscle. Note the occlusion of arterioles with retracted masses of a fibrinoid-like protoplasm, and the marked edema of the myocardium.

The temperature was 100.6° F.; pulse, 112; respirations, 28; blood pressure, 120/60 mm. of Hg. The patient was an obese, obviously acutely ill white female with a definite yellow tint to the skin and icteric sclerae. The sensorium was clouded and she was unable to speak distinctly. Ecchymotic areas were scattered over her body. Numerous petechiae were present over the legs. The left border of the heart extended to the anterior axillary line and a rough systolic murmur was audible over

the entire precordium. The liver was palpable just below the right costal margin and the spleen was not palpable. The lower right leg was encased in a boot-shaped cast.

The hemoglobin was 6.25 gm.; hematocrit, 21 per cent; red cell count, 2.3 million; MCV 91, MCH 27.2, MCHC 29.5; corrected sedimentation rate, 16; white cell count, 17,800, with 4 per cent myelocytes, 5 per cent juveniles, 77 per cent neutrophils, 10 per cent lymphocytes and 4 per cent monocytes. The platelets were markedly reduced on smear and the direct platelet count was 17,000. There were 23 nucleated red cells per 100 white cells. The reticulocyte count was 3.9 per cent. The prothrombin time was 18 seconds (control, 15 seconds); bleeding time, 2 minutes and

FIG. 2. Heart. Miliary infarctions, showing two of the many similar infarcts throughout the myocardium.

10 seconds; clotting time, 5 minutes; the tourniquet test was strongly positive. Blood chemical data were as follows: fasting blood sugar, 120 mg. per cent; nonprotein nitrogen, 29.7 mg. per cent; albumin, 4.2 gm. per cent; globulin, 3.0 gm. per cent; icterus index, 31.6; serum bilirubin, 1.2 mg. per cent indirect. The urine was cloudy and dark, with a specific gravity of 1.015, 2 plus albumin, no sugar, and many white cells on microscopic examination. Catheterized urine culture grew out *Escherichia coli*. The urine urobilinogen test was strongly positive, and the urine was slightly positive for bile.

Aspirated sternal marrow disclosed no abnormality of the white cell series. Megakaryocytes were numerous but no platelet formation was seen. The proportion of nucleated red cells was greatly increased. The red cells disclosed striking

anisocytosis, and many macrocytes and spherocytes were present. Sections of the fragments of marrow obtained by aspiration unfortunately did not include any arterioles. The "L.E." cell preparation was negative on two occasions. There was low voltage in the standard limb leads of the electrocardiogram, inverted T waves in Leads I, aVL, and all of the chest leads. The T waves were low in Leads II and aVF. The blood group was A_1 Rh_0 positive. No Rh or Hr antibodies were demonstrable by the serum-albumin methods. The direct and indirect Coombs' tests were negative. Osmotic fragility began at 0.60 per cent (control, 0.48 per cent) and was complete at 0.27 per cent (control, 0.33 per cent).

Therapy consisted of penicillin, streptomycin and Gantrisin initially. The latter drug was discontinued on the third day because of the appearance of gross hematuria.

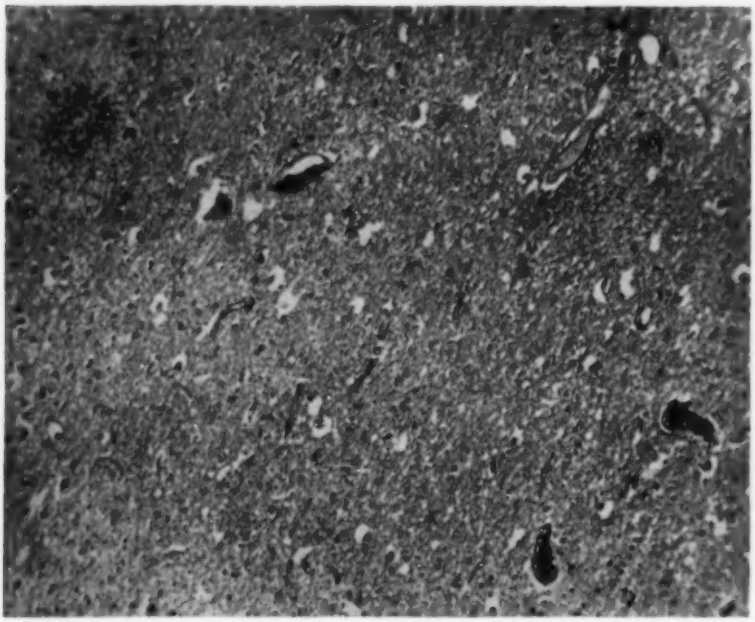

FIG. 3. Brain. Occluded arterioles and a focal necrotic area typical of many similar cerebral lesions.

The fever declined over a period of several days to normal, and the urinary tract infection cleared. Within the first five hospital days the patient received 2,500 c.c. of whole blood, the hemoglobin rising to 9.25 gm. However, her sensorium failed to improve and she became totally aphasic. Twitching movements of the left side of the face, left arm and left leg were noticed at times. On the eleventh hospital day ACTH therapy was begun, 40 mg. intravenously every day until death. There was no change in the general clinical condition, and four days after the start of ACTH therapy the platelet count was 20,000, having been 17,000 the day it was started. On the sixteenth hospital day fever developed, reaching 105° F. within 24 hours. High fever and progressive coma continued until death on the eighteenth hospital day (the seventh day of corticotrophin therapy).

Autopsy was performed 12 hours after death. The body was that of a well developed, well nourished elderly white female with moderate icterus of the skin and sclerae. There was slight pitting edema of the extremities. The heart weighed 340 gm., and the myocardium was pale and flabby. Petechiae were seen over the right atrium. The liver weighed 1,700 gm., and the surface was smooth. The spleen weighed 220 gm. and appeared grossly normal. The adrenals were small and soft, and appeared to have undergone postmortem autolysis. The kidneys each weighed approximately 160 gm. and grossly appeared normal. On removal of the brain an excessive amount of fluid was noted, and the surfaces of both cerebral hemispheres appeared somewhat gelatinous.

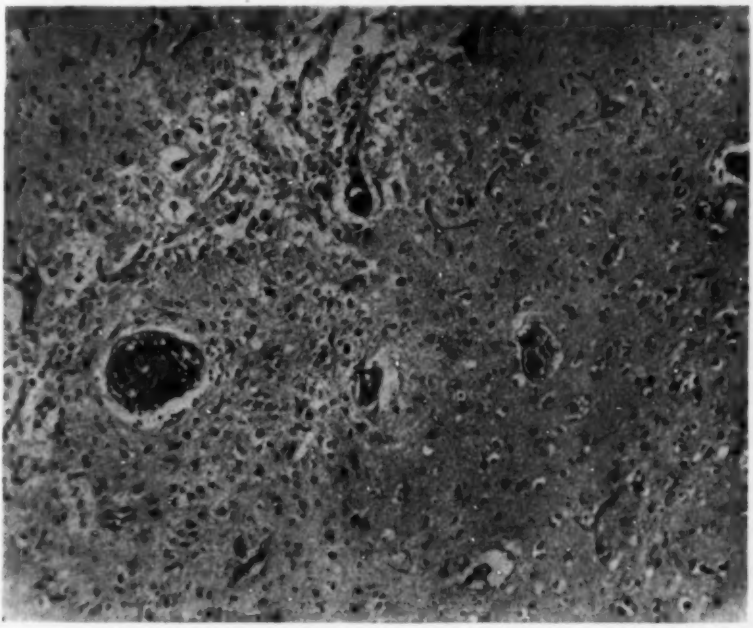

FIG. 4. Brain. Arteriolar occlusion with recanalization along the retracted plug, and an area of early cerebral infarction. This represents one of many similar lesions.

Microscopically the capillaries and the arterioles throughout the heart, brain, liver, kidneys, and adrenals and spleen were plugged with a homogeneous pink-staining globular material. There was marked edema of the myocardium, with areas of petechial myocardial degeneration. These areas of degeneration were not associated with any leukocytic reaction. There was patchy atelectasis of the lungs, marked capillary engorgement and patchy pneumonic interstitial reaction. The liver cells, some of which were bile stained, disclosed extreme vacuolation. Polymorphonuclears were not infrequent along the sinusoids. The portal tracts were conspicuous for the collection of lymphocytes. In some of the portal vessels there was some of the globular material present in the capillaries and arterioles elsewhere. The tubules of the kidneys were conspicuously dilated. The lining epithelium was granular and there was disintegration of the cells along the course of the conducting tubules.

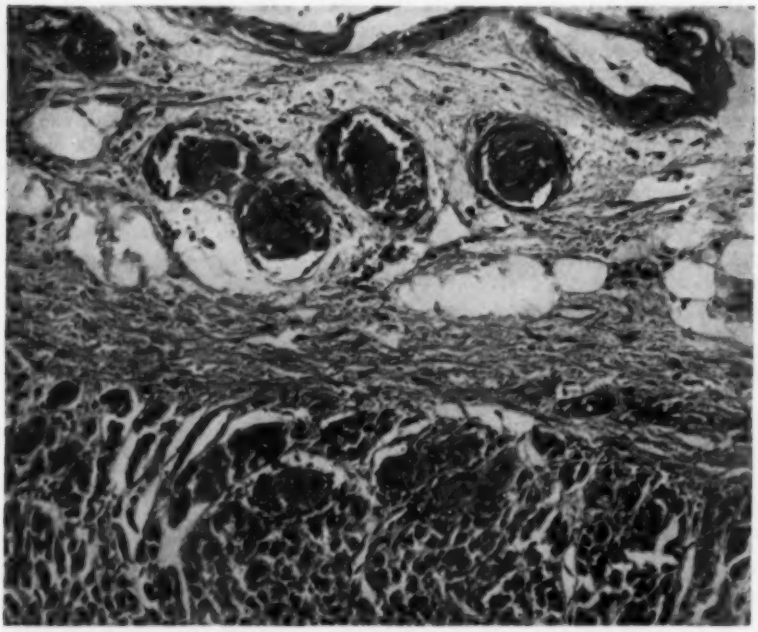

FIG. 5. Adrenal cortex. The occluded arterioles are seen in the adrenal cortex, as well as in the peritoneal fascia. The number of capillaries seen partially occluded is generalized.

The glomerular tufts were contracted within large dilated Bowman's capsules. There was no leukocytic reaction. Casts were seen, some bile stained. Neither hemorrhage nor inflammation was present in the adrenals. In the spleen there was a conspicuous accumulation of polymorphonuclears, although there was no massing of these cells. The arterioles along the Malpighian bodies presented marked thickening and hyalinization of the walls, and many of these arterioles contained the homogeneous pink globular substance. Some of the larger arterioles appeared obliterated, with small spaces along the perimeter which allowed the circulation to pass. There was marked engorgement of the sinusoids with blood, and mixed with the blood were macrophages containing debris. Conspicuous reticuloendothelial reaction was present. No myeloid tissue was encountered in the spleen. There was characteristic arachnoid edema about the brain, with an accumulation of macrophages within the arachnoid. Small patches of disintegration of brain substance were found. These areas were not associated with any reaction such as hemorrhage or leukocytes.

The final anatomic diagnosis was: thrombotic thrombocytopenic purpura characterized by a generalized plugging of arterioles, and characterized clinically by hemolytic anemia, cerebral manifestations and thrombocytopenic purpura.

DISCUSSION

This case presents several most interesting features. Smears of the aspirated bone marrow contained numerous megakaryocytes, but no platelet "budding" was

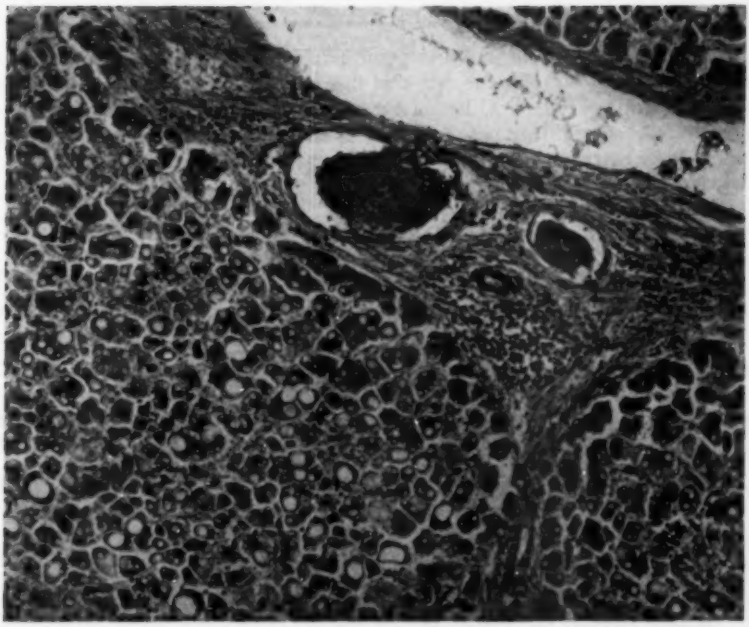

FIG. 6. Liver. Occlusions of hepatic arterioles. Note retraction of the occluding substance, and a marked fatty vacuolation of the liver cells.

present. This defect of platelet formation was strikingly similar to that seen in the usual cases of "idiopathic" thrombocytopenic purpura. It is difficult to fit this into the theory that the platelets are used to form the peculiar pink globular material in the arteriolar thrombi. The electrocardiogram disclosed low voltage and diffuse T wave changes, probably correlated with the areas of myocardial degeneration seen at autopsy. An extensive study was made to determine if there was an "immune type" antibody present that might account for the hemolytic anemia. No antibodies were demonstrable with the serum, albumin and Coombs' tests. It has been thought that this disease might belong to the "collagen vascular" group, particularly in that some cases of this syndrome may have been associated with disseminated lupus erythematosus.[5] For this reason the negative "L.E." preparation is of great interest. Unfortunately, sections of the bone marrow fragments obtained by aspiration did not contain arterioles; therefore, we could not verify the diagnosis ante mortem as reported by Cooper et al.[4]

It is obvious that therapy in this case was of no avail. Because of the possibility that this may be one of the collagen vascular diseases, it was thought that ACTH or cortisone therapy might be useful. Despite therapy for seven days with intravenous corticotrophin, the course of the disease was unchanged. It is possible that this therapy was initiated too late, and such treatment should be tried in other cases to further determine its value.

SUMMARY

A case of thrombotic thrombocytopenic purpura diagnosed ante mortem has been presented. It is apparent that this disease may be diagnosed if the triad of thrombocytopenic purpura, hemolytic anemia and neurologic manifestations is encountered. Certain studies of interest in the understanding of this syndrome, including bone marrow aspiration, Coombs' test and "L.E." cell preparation, are reported. ACTH therapy did not alter the course of the disease.

ACKNOWLEDGMENT

We wish to express our gratitude to Dr. Walter C. Merkel, Pathologist and Director of Laboratories, Union Memorial Hospital, for his assistance and advice in the preparation of this paper. We also wish to thank Dr. C. Lockard Conley, Johns Hopkins Hospital, for interpreting the bone marrow studies in this case.

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EDITORIAL

PATHOGENETIC MECHANISMS IN IDIOPATHIC THROMBOCYTOPENIC PURPURA

THIS syndrome has long been a puzzling problem both as to its underlying cause and its pathogenesis. Recent studies which reveal the mechanisms apparently concerned in some of these cases constitute important contributions to this subject. These "idiopathic" cases must be distinguished from primary diseases of the bone marrow, such as acute leukemia or aplastic anemia, in which the lack of platelets is a subsidiary phenomenon. It is also customary to distinguish them from those cases for which there is a demonstrable cause, such as a hypersensitive reaction to certain drugs, although in other respects clinically they may be virtually indistinguishable. It is becoming clear, however, that the residual cases of idiopathic thrombocytopenic purpura do not constitute a single disease entity but include a variety of types of presumably different origin.

The dearth of platelets in this syndrome has been explained both by inadequate formation and by increased consumption or destruction and either or both of these processes have been attributed to a pathologic overactivity of the spleen. There is no lack of megakaryocytes in the marrow, and if reduced production is the primary difficulty, it must be due to some functional injury or inadequacy of these cells. Among current investigators, this view has been upheld particularly by Dameshek and his associates,[1] who described abnormalities in the appearance of the megakaryocytes which suggested a failure to produce platelets. This has been attributed to a hormonal product of the spleen, since the appearance of these cells reverted to normal after splenectomy in successful cases. Accelerated destruction, on the other hand, has been maintained by others, including Doan and Wiseman,[2] who believe that the platelets (with or without previous injury in the circulation) are sequestered and destroyed in the spleen. Although in specific instances strong evidence can be adduced to support both views, there is increasing evidence that platelets may suffer direct injury from substances present in the circulating blood.

The direct study of the platelets has been greatly hampered by the instability of these structures and by their tendency quickly to clump and disintegrate when removed from the vessels. This has been partly overcome by the development of new technical methods which, with meticulous care, make it possible to obtain relatively stable suspensions which are suitable for investigative procedures.

The presence in the plasma of an agent injurious to the platelets may be

[1] Dameshek, W., and Miller, E. B.: The megakaryocytes in idiopathic thrombocytopenic purpura, a form of hypersplenism, Blood **1**: 27–52, 1946.
[2] Doan, C. A.: Hypersplenism, Bull. New York Acad. Med. **25**: 625–650, 1949.

demonstrated in several ways. Normal platelets, transfused in large quantities into a patient whose plasma contains such an agent, may be eliminated within a few hours, regardless of whether splenectomy has been performed. In cases of secondary thrombocytopenia, such as acute leukemia, the increase in platelet count following transfusion may be maintained in some degree for three to six days, a period which is equal to the probable normal life span of the platelets.

In some cases of idiopathic thrombocytopenic purpura the presence of a toxic agent can be shown by the injection of such plasma into normal recipients. Harrington et al.[3] showed that although normal plasma may cause a transient moderate fall in platelets, plasma from an active case of idiopathic thrombocytopenic purpura may cause a rapid and profound drop. This observation has been confirmed by Stefanini, Dameshek et al.[4] who observed purpura and bleeding in the recipients and persistence of the toxic agent in their circulation for about two weeks. The rapidity of the drop indicated direct injury to the platelets in the circulation.

Presumptive evidence of a substance toxic to the platelets has been obtained by a study of infants of mothers with idiopathic thrombocytopenic purpura. Epstein et al.[5] studied five such women during seven pregnancies and observed thrombocytopenia in six infants with purpura in five. In all of them the platelets subsequently rose to normal, usually within a few months. In 39 cases collected from the literature, in about half of the infants born alive, transient thrombocytopenia and purpura were recorded. This was independent of whether splenectomy had been performed in the mother. The observations suggest that some toxic or inhibitory substance, independent of the spleen, is transferred through the placenta to the fetus but is eventually eliminated. This is not a true inherited defect, since the development of the chronic form of the disease in these children is relatively very rare.

Allergic hypersensitiveness to certain drugs may result in the development of clinically typical acute thrombocytopenic purpura if such drugs are administered to sensitive subjects. Of these, cases of sensitiveness to Sedormid[6] and to quinidine have been most carefully studied. Hirsch and Dameshek[7] in one case twice produced an attack by administering a few doses of quinidine. The megakaryocytes in the marrow showed the same

[3] Harrington, W. J., Minnich, V., Hollowingsworth, J. W., and Moore, C. V.: Demonstration of a thrombocytopenic factor in the blood of patients with idiopathic thrombocytopenic purpura, J. Lab. and Clin. Med. **36**: 1–10, 1951.

[4] Stefanini, M., Dameshek, W., Chatterjea, J. B., Adelson, E., and Mednicoff, I. B.: Studies of platelets. IX. Observations on the properties and mechanism of action of a potent platelet agglutinin detected in the serum of a patient with idiopathic thrombocytopenic purpura (with a note on the pathogenesis of the disease), Blood **8**: 26–64, 1953.

[5] Epstein, R. D., Lozner, E. L., Cobbey, T. S., Jr., and Davidson, C. S.: Congenital thrombocytopenic purpura, purpura hemorrhagica in pregnancy and in the new born, Am. J. Med. **9**: 41–56, 1950.

[6] Ackroyd, J. F.: The mechanism of the reduction of clot retraction by Sedormid in the blood of patients who have recovered from Sedormid purpura, Clin. Sc. **8**: 235–267, 1949.

[7] Hirsch, E. O., and Dameshek, W.: Thrombocytopenic purpura due to allergy to quinidine. Study of the mechanism of thrombocytopenia, Am. J. Med. **9**: 828–833, 1950.

abnormalities (suggesting inhibition of platelet formation) which they have described in idiopathic thrombocytopenic purpura, but the fall in platelet count was so precipitous that destruction and removal from the peripheral blood must be assumed.

Larson [8] in a closely similar case more precisely defined the nature of the toxic substance. The addition of minute amounts of quinidine to the patient's blood inhibited clot retraction but did not affect clot retraction of normal blood. If, however, some of the patient's serum was also added to the normal blood, clot retraction was inhibited. The reaction was regarded as allergic, the quinidine acting as a haptine and combining with some protein constituent of the plasma of the patient to form the toxic substance (antibody). The mechanism of its action on the platelets was not demonstrated, but the precipitous fall (from 325,000 to 25,000 in two hours after 0.2 gm.) indicated that the injury must occur in the peripheral circulation.

An allergic reaction of this type can explain only a limited number of cases of thrombocytopenic purpura. That other types of substances in the plasma may directly damage the platelets is indicated by the observations of Evans et al.[9] and of Stefanini and associates.[4] Evans stressed the resemblances of idiopathic thrombocytopenic purpura to acquired hemolytic anemia, in which "autoantibodies" active on the red cells can usually be demonstrated, and he pointed out the frequent association of the two processes. He suggested that a similar type of auto-antibody may injure the platelets, and he reported finding platelet agglutinins in some cases. Stefanini et al.,[4] utilizing highly specialized technics, have obtained more direct evidence of this, particularly in one patient who was intensively studied. This was a woman of 60, with typical chronic idiopathic thrombocytopenic purpura of one to two years' duration, of moderate severity, who later obtained substantial improvement but gave an inadequate response to splenectomy. They found that the transfusion into this patient of normal platelets in large quantities increased the platelet count significantly, but only while the transfusion was in progress. Her plasma caused severe thrombocytopenia with purpura in normal subjects, their circulating platelets and megakaryocytes showing qualitative abnormalities similar to those of the patient, and the toxic agent continuing to be demonstrable in their blood for about two months.

When stable suspensions of normal platelets were exposed to her plasma, even in high dilution, they were promptly and markedly agglutinated, whereas normal serum was inactive. Lysis of the platelets was not demonstrated. The titer was not notably influenced by any treatment given, except that it was slightly and transiently reduced after splenectomy. The agglutinins could be removed by repeated absorption with normal platelets.

Additional evidence of an "antibody" was obtained by the use of Coombs'

[8] Larson, R. K.: The mechanism of quinidine purpura, Blood **8**: 16–25, 1953.
[9] Evans, R. S., et al.: Primary thrombocytopenic purpura and acquired hemolytic anemia; evidence for a common etiology, Arch. Int. Med. **87**: 48–65, 1951.

anti-human globulin serum (obtained from rabbits which have received injections of human globulin). Normal human red cells and according to Stefanini et al., normal human platelets, if washed free from plasma, will not be agglutinated by such a serum. If, however, such red cells have absorbed some human globulin, such as an incomplete anti-Rh agglutinin, they will be specifically agglutinated by the Coombs serum. The positive reaction indicates the presence of human globulin on the surface of the red cells, and by inference an antibody, since this is the only form in which globulin can stick to the cell after adequate washing. It was found that Coombs' serum specifically agglutinated suspensions of washed platelets obtained under the following circumstances: (1) suspensions of platelets from the patient, particularly during a transient rise in the platelet count after splenectomy; (2) normal platelets which had been exposed to the patient's serum in vitro; (3) platelets from normal subjects who had received an injection of the patient's plasma, for a period of about two weeks after such injection.

Although the use of Coombs' serum hitherto has been restricted essentially to experiments with red blood cells, theoretically it should be equally applicable to platelets. Caution is necessary in the interpretation of such experiments, since platelets are fragile and cannot withstand as vigorous manipulations and numerous washings as can red cells. These experiments, however, seem to have been rigorously controlled, and the assumption that the injurious agent is an "antibody" seems justified although perhaps not conclusively demonstrated. The underlying cause, however, the source of the stimulus that produced the antibody, remains a mystery.

It would be tempting to explain the temporary benefit obtained in some cases of idiopathic thrombocytopenic purpura by the administration of ACTH or cortisone as due to an inhibition of the formation of such autoantibodies. It is possible that further study may support such an assumption. In the case just reviewed, however, administration of these hormones had no significant effect on either the titer of the agglutinin or the condition of the patient.

At present there is no proof that all or even a large proportion of the cases of idiopathic thrombocytopenic purpura can be explained by the production of autoantibodies. In Stefanini's series, 35 cases were tested by injection of their plasma into normal subjects and only one other gave a comparably marked response. In 12 others the thrombocytopenia produced was more protracted than that with normal serum. It seems probable, however, that this procedure would not be a very sensitive means of detecting lower concentrations of antibody and that better methods may reveal them more frequently, as was the case in the early studies of acquired hemolytic anemia. Although these observations tend to assign to the spleen a secondary rôle in the pathogenesis of idiopathic thrombocytopenic purpura, it remains a fact that splenectomy is effective and is the only really effective treatment in 60 per cent or more of the chronic cases of the disease.

P. W. C.

REVIEWS

Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches into the Function of Emotional Excitement. By WALTER B. CANNON, M.D., S.D., LL.D., George Higginson Professor of Physiology in Harvard University. 404 pages; 14 × 21 cm. Charles T. Branford Company, Boston. 1953. Price, $5.00.

This is apparently a reprint of the second edition, which appeared in 1929. Careful reading did not disclose any new material that might have been added after Cannon's death in 1945, and there are no citations in the bibliography later than 1929. Nevertheless, many parts of the book are as timely as if they appeared yesterday. It is written in a style of almost classical simplicity, accurate and precise enough to satisfy the specialist and yet easily understood by the general reader. In fact, its writing may well be taken as a model of its kind.

It comes as a bit of a shock to realize that even as late as 1929 the physiological effects of emotional activity were just beginning to be understood. Cannon published the first edition of this book in 1915 and in the intervening years expanded the scope of his studies until the outlines of his "emergency theory" were well filled in by 1929. Thus one of the earliest contacts between the physiologist and the psychologist was established and it is certainly no exaggeration to say that these investigations had a profound influence upon the subsequent development of psychosomatic medicine.

Included in the book is an analysis of the relationships between such things as the level of blood sugar, coagulation of the blood, number of circulating red cells, digestion, heart rate, blood pressure, hunger, thirst and last, but by no means least, the activity of the adrenal medulla and emotional activity. Cannon's conclusions in regard to these matters are now taken for granted. In fact, they are taught in high school biology classes and have become a part of our scientific heritage, integrated into the general body of scientific knowledge in such a way that their origin and source are partly forgotten.

Today, of course, our knowledge has advanced considerably beyond the boundaries established in 1929, but much of what we now know was anticipated by Cannon and developed in the subsequent work of his own students. For instance, Cannon saw the significance of the thalamic regions in relation to autonomic function. It would be a lengthy task to recount all of the physiological advances which had their beginnings in Cannon's studies, but the sum total would be impressive.

In other areas the book is dated. Cannon's concern with such things as the James-Lange theory of emotions and his arguments for a physical substitute for war have little but historical interest. However, such speculations serve as an illuminating example of how hypotheses, even when wrong, can and do add to the advancement of understanding. Even so, making due allowance for a different point of view in these days of nuclear fission and fusion, this summation of his experiments still stands as a monument to his genius. As does all good scientific reporting, the book has about it a timeless quality which may well keep it alive and fresh for years to come.

DIETRICH C. SMITH

Diuretic Therapy. By ALFRED VOGL, M.D. 248 pages; 15.5 × 23.5 cm. The Williams and Wilkins Co., Baltimore. 1953. Price, $5.00.

As Dr. Fishberg says in his foreword, such a book by such a man is indeed "an event." The author of this excellent monograph has had an intimate and happy

association with the diuretics, for it was he who, as a medical student in 1919, first noted the diuretic action of an organic mercurial being used as an anti-syphilitic agent. This chance observation led to the greatest advance in the therapy of heart failure since the introduction of digitalis a century and a half before—the development of the mercurial diuretics. Dr. Vogl therefore has an intense personal interest in the subject and his enthusiasm is communicated to the reader.

On first inspection the subject "diuretic therapy" might appear to possess only limited appeal. Yet any physician who handles patients with heart failure, cirrhosis of the liver, nephrosis, or any other edematous syndrome—and who does not?—should find this a valuable guide and reference work. It is an unusually well written book and fills a needed gap; for it remains unfortunately true that, despite the recent spate of work on edema and the inseparable subject of diuresis, most textbook accounts of these subjects are regrettably brief and leave one with a not very clear conception of the rationale and principles of diuretic therapy.

This text begins with a brief chapter on the pathogenesis and principles of treatment of edema, which contains a good summary of current concepts of edema formation especially in congestive failure. In the next chapter indications for diuretic therapy are in turn discussed. The pharmacological actions and relative effectiveness of the various diuretic drugs are dealt with next. The diuretics covered in this chapter are the osmotic, acidifying and xanthine compounds; the uracils; decholin; the mercurials and the salts of bismuth. A short but important chapter on antidiuretic substances follows, in which the antidiuretic action of morphine and other narcotics is stressed. The last two chapters comprise two thirds of the text and deal with the practice of diuretic therapy. In the first of these chapters diuretic adjuvants, such as rest, sodium restriction, exchange resins and the mechanical removal of fluid, are discussed. In the final and longest chapter, the use of the three most important groups of actual diuretic drugs—the mercurials, xanthines and acidifying salts—is taken up in detail. The work is documented with an up-to-date bibliography of over 700 references.

This book should prove of great value to general practitioners, internists, cardiologists and resident staffs, many of whom will be surprised how much there is to learn about the intelligent use of diuretics. Dr. Vogl's contribution achieves an unusual combination of virtues among medical texts—it is at the same time both extremely practical and absorbing reading.

H. J. L. M.

Tumors of the Thyroid Gland (Atlas of Tumor Pathology, Section IV, Fascicle 14). By SHIELDS WARREN, M.D., Professor of Pathology, Harvard Medical School, and WILLIAM A. MEISSNER, M.D., Assistant Professor of Pathology, New England Deaconess Hospital, Boston. 97 pages; 20 × 26 cm. (paperbound). Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C. 1953. Price, $1.75.

The authors of this section, IV, being fully aware of the taxonomic difficulties and controversies that surely are to be encountered in studies of thyroid gland tumors, by a commendable schema have reduced these hazards to a minimum. At the outset, they present the pseudo-tumors or nodular hyperplasia, cysts and chronic inflammatory lesions that are peculiar to the thyroid gland.

The benign and malignant tumors are presented following a convenient and revealing outline. After the subject, synonyms and related terms, definition of the subject, gross and microscopic descriptions, etiology and histogenesis, natural history, prognosis, differential diagnosis and treatment are given. In appropriate sections

degenerative and vascular changes that may occur to alter the apparent growth rate and likelihood of malignant change are set forth. The use of radioactive iodine in diagnosis and treatment of thyroid tumors and relationship of structure and probable iodine uptake are mentioned in the various tumor sections and briefly enlarged upon in a special section on radioiodine and radioautographs. The sections on gross and microscopic appearances are lucid and supported generously by well executed photomicrographs and portrayals of gross specimens.

In the opinion of this reviewer, the pathologist, internist, or surgeon can find in this fascicle a ready reference to tumors of the thyroid gland.

D. L. R.

Spleen Puncture. By SVEN MOESCHLIN, M.D., Privatdozent, University Medical Clinic, Zurich, Switzerland; translated by A. PINEY, M.D. 229 pages; 16 × 25 cm. Grune & Stratton, Inc., New York. 1951. Price, $5.50.

Splenic puncture as a diagnostic aid in cases of idiopathic splenomegaly has been employed by European investigators for many years. In North America the procedure has been a rarity until recently, and at present spleen punctures are common only in the larger medical teaching and research centers. In view of the increasing interest in splenic aspirates, the present monograph is timely as a reference for those interested in lymphomatous disease.

The first edition of Dr. Moeschlin's work was published in Switzerland in 1947. The present printing is an English translation of the Swiss edition with added illustrations and pertinent material gathered from the literature since the original publication. The major portion of the book is based on the clinical observations of the author in 300 splenic punctures performed between 1939 and 1949. Many color illustrations of splenograms typical of specific clinical entities enhance the value of the printed text.

In addition to discussing indications and technic of splenic puncture, the author attempts to dispel the fear of untoward effects arising from the procedure by advocating a few cardinal rules. In summary, the rules are: only an enlarged spleen should be punctured and then during deep inspiration; puncture is contraindicated in the presence of a hemorrhagic tendency, recent septic splenomegaly or in an unconscious patient.

In the opinion of the author, splenic puncture combined with bone marrow and lymph node aspiration provides a most complete estimate of the extent and location of lymphomatous disease. With such a survey, the present knowledge of etiology and therapy of lymphomatous diseases should be considerably advanced.

The monograph is recommended as a reference source to the physician particularly interested in the field of hematology and diseases of the reticulo-endothelial system.

J. B. W.

Psychiatric Dictionary. By LELAND E. HINSIE, M.D., and JACOB SHATZKY, Ph.D. 2nd Ed., with Supplement. 781 pages; 16 × 24 cm. Oxford University Press, New York. Price, $15.00.

Here, in one handsomely bound and beautifully printed edition, are the *Psychiatric Dictionary* of 1940 and the new 221 page supplement. This supplement is also available separately at lower cost for those who already have the 1940 edition.

The new supplement represents an attempt to add words omitted from the old edition, and to account for some of the more recently introduced psychiatric terms. The authors have continued the wise practice of making reference to the literature from whence they derived their definitions. Thus, any criticism must be leveled

at the selection of words to be defined and at the sources selected as authoritative. I'm sure that others besides this reviewer had hoped that the old bias in favor of descriptive and psychoanalytic terminology would be supplanted by terms from psychology, physiology and other allied disciplines. Although the supplement includes Sullivanian terms like "parataxic distortion" as well as definitions of physical therapies such as "electronarcosis," a quotation from Freud still defines "entropy." Much of the pertinent nomenclature from neurophysiology, communication theory, etc., is completely omitted. This criticism, however, actually becomes a plea for still another supplement. It would be easy to take issue with many of their definitions, but no dictionary is perfect. In a field as beset by vague meanings as is psychiatry today, this work renders an inestimable service. Student, teacher and practitioner alike will find this volume invaluable, both for its definitions and for its references.

E. C.

X-Ray Sieve (Grid) Therapy in Cancer: A Connective Tissue Problem. By BENJAMIN JOLLES, M.D., D.M.R., Consultant Radiotherapist, Physician i/c Radiotherapy Department, General Hospital, Northampton, Formerly Duchess of Bedford Research Fellow in Medical Radiology, The Middlesex Hospital Medical School, London, etc. 192 pages; 14 × 22 cm. Little, Brown and Company, Boston, Mass. 1953. Price, $6.00.

The title of this book is somewhat misleading as to its contents. Instead of a thorough discussion of sieve (grid) therapy, as implied by the title, approximately two thirds of the subject matter is concerned with radiobiology, especially the rôle of connective tissue in biological processes. Throughout, the author stresses his own ideas on radiobiology, tissue response, dosage levels, etc.

The information on sieve therapy obtained from this book will be of little value to the clinical radiologist as the author has far too little material from which to publish a book. His experience is based on 54 cases of cancer treated by this method, with no extensive series of cases referable to any one structure or organ. In our present radiology journal any article on this subject usually deals with a larger series of patients. Apparently he tried to replace this lack of material with a prolonged discussion of the rôle of connective tissue in radiobiology.

J. M. D.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Annual Review of Medicine. Volume 4. WINDSOR C. CUTTING, Editor, Stanford University School of Medicine; and HENRY W. NEWMAN, Associate Editor, Stanford University School of Medicine. 452 pages; 23 × 15.5 cm. 1953. Annual Reviews, Inc., Stanford, California. Price, $6.00.

Bioassay of Anterior Pituitary and Adrenocortical Hormones. Volume V. Ciba Foundation Colloquia on Endocrinology. General Editor for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch.; Assisted by MARGARET P. CAMERON, M.A., A.B.L.S. 228 pages; 21 × 14 cm. 1953. Little, Brown & Company, Boston. Price, $6.00.

Chemical Physiology of Contraction in Body and Heart Muscle. By A. SZENT-GYÖRGYI, The Institute for Muscle Research, at the Marine Biological Laboratory, Woods Hole, Massachusetts. 135 pages; 23.5 × 15.5 cm. 1953. Academic Press, Inc., New York. Price, $4.80.

Child Psychology: Summary of Growth and Development with Review Questions and Answers. Keyed to Standard Textbooks. College Outline Series. By LESTER D. CROW, Department of Education, Brooklyn College, and ALICE CROW, Department of Education, Brooklyn College. 267 pages; 21 × 13 cm. (paper-bound). 1953. Barnes & Noble, Inc., New York. Price, $1.50.

Cornell Conferences on Therapy. Volume Six. Edited by HARRY GOLD, M.D., Managing Editor; DAVID P. BARR, M.D., MCKEEN CATTELL, M.D., FRANK C. FERGUSON, JR., M.D., FRANK GLENN, M.D., and GEORGE READER, M.D. 287 pages; 21 × 14 cm. 1953. The Macmillan Company, New York. Price, $4.00.

Cybernetics: Circular Causal and Feedback Mechanisms in Biological and Social Systems: Transactions of the Ninth Conference, March 20–21, 1952, New York, N. Y. Edited by HEINZ VON FOERSTER, Department of Electrical Engineering, University of Illinois, Champaign, Illinois; Assistant Editors: MARGARET MEAD, American Museum of Natural History, New York, N. Y., and HANS LUKAS TEUBER, Department of Psychiatry and Neurology, New York University College of Medicine, New York, N. Y. 184 pages; 24 × 16 cm. 1953. Sponsored by Josiah Macy, Jr. Foundation, New York, N. Y. Price, $4.00.

The Diabetic Neuropathies: A Monograph in the Bannerstone Division of American Lectures in Endocrinology. Publication Number 151, American Lecture Series. By JOSEPH I. GOODMAN, M.D., SIEGFRIED BAUMOEL, M.D., LEONARD FRANKEL, M.D., LOUIS J. MARCUS, M.D., and SIGMUND WASSERMANN, M.D. 138 pages; 22 × 14.5 cm. 1953. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $4.75.

Expert Committee on Influenza: First Report. World Health Organization Technical Report Series No. 64. 32 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 20 cents.

Expert Committee on Venereal Infections and Treponematoses: Fourth Report. World Health Organization Technical Report Series No. 63. 84 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 55 cents.

First International Symposium on Yaws Control. World Health Organization Monograph Series No. 15. 418 pages; 24 × 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $4.50.

Medicine. Volume One: The Patient and His Disease. 2nd Ed. A. E. CLARK-KENNEDY, M.D., F.R.C.P., Fellow of Corpus Christi College, Cambridge, etc. 410 pages; 24.5 × 15.5 cm. 1953. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Pituitary Chromophobe Adenomas: Neurology, Metabolism, Therapy. A Clinical Study of the Sellar Syndrome. By JOHN I. NURNBERGER, M.D., Research Associate, The Institute of Living, and Assistant Clinical Professor of Medicine (Neurology), Yale University School of Medicine; and SAUL R. KOREY, M.D., Associate Professor of Neurology, The School of Medicine, Western Reserve University. 282 pages; 23.5 × 15.5 cm. 1953. Springer Publishing Company, Inc., New York. Price, $7.00.

The Pluripotency of the Hypophyseal Hormones and the Consequences for Endocrinology and Cancerology. By DR. JULES SAMUELS, Specialist for Endogenous Endocrinotherapy, Director of the Central Institution for the Samuels-Therapy, Amsterdam. 296 pages; 25 × 16 cm. 1953. N. V. Cycloscoop, Amsterdam. Price, $10.00.

Proceedings of the Kessler Institute for Rehabilitation: Clinic on Congenital Amputations. Editor: HENRY H. KESSLER, M.D.; Assistant Editor: TRUDY DRUCKER. 35 pages; 23 × 15.5 cm. (paper-bound). 1953. Kessler Institute for Rehabilitation, West Orange, N. J. Price: No charge; published and mailed as a professional educational service of the Kessler Institute.

St. Thomas's Reports. Second Series. Volume VIII. Editorial Committee: DR. R. DALEY, DR. H. K. GOADBY, MR. R. W. NEVIN, DR. J. S. RICHARDSON, MR. R. B. K. RICKFORD, and DR. H. J. WALLACE. 148 pages; 25.5 × 16 cm. 1952. St. Thomas's Hospital, London. Price, 10s. 6d.

Sectional Radiography of the Chest. By IRVING J. KANE, M.D., Consultant in Chest Diseases, United States Naval Hospital, St. Albans, N. Y., etc.; Foreword by EDWARD D. CHURCHILL, M.D. 154 pages; 26 × 17 cm. 1953. Springer Publishing Company, Inc., New York. Price, $7.50.

The Surgery of Infancy and Childhood: Its Principles and Techniques. By ROBERT E. GROSS, M.D., D.Sc., William E. Ladd Professor of Children's Surgery, The Harvard Medical School, etc. 1,000 pages; 25.5 × 18 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $16.00.

Surgery of the Pancreas. By RICHARD B. CATTELL, M.D., Surgeon, The Lahey Clinic, etc.; and KENNETH W. WARREN, M.D., Surgeon, The Lahey Clinic, etc. 374 pages; 25.5 × 16.5 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $10.00.

Therapeutics in Internal Medicine. 2nd Ed. By EIGHTY-FOUR AUTHORITIES; Edited by FRANKLIN A. KYSER, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School, Chicago, etc. 830 pages; 27 × 18.5 cm. 1953. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $15.00.

Twenty-five Years of Sex Research: History of the National Research Council, Committee for Research in Problems of Sex, 1922–1947. By SOPHIE D. ABERLE, Member of the National Science Board of the National Science Foundation; and GEORGE W. CORNER, Carnegie Institution of Washington. 248 pages; 21.5 × 14 cm. 1953. W. B. Saunders Company, Philadelphia. Price, $4.00.

COLLEGE NEWS NOTES

New Life Members

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the list in last month's issue of this journal:

Dr. Ramon J. Sifre, Santurce, San Juan, P. R.
Dr. Paul S. Caplan, Pittsburgh, Pa.
Dr. John Goodrich Smith, Rocky Mount, N. C.
Dr. Howard R. Bierman, San Francisco, Calif.

A. C. P. Annual Session Meeting Dates and Places

The American College of Physicians will hold its Thirty-Fifth Annual Session at Chicago, April 5–9, 1954, with Headquarters at the Conrad Hilton Hotel. Dr. LeRoy H. Sloan, 5800 Stony Island Ave., Chicago 37, Ill., as President of the College, will be in charge of the Program of General Sessions and Morning Lectures or Symposia. Dr. Howard Wakefield, 122 S. Michigan Ave., Chicago 3, Ill., as General Chairman, will be in charge of the program of Clinics, Panels, Clinical-Pathological Arrangements and Entertainment.

The Thirty-Sixth Annual Session of the College will be held at Philadelphia, April 25–29, 1955, with Headquarters at the Municipal Auditorium. Dr. Cyrus C. Sturgis, University of Michigan Medical School, Ann Arbor, Mich., as President, will be in charge of the Program of General Sessions and Morning Lectures or Symposia. Dr. Thomas Durant, Temple University School of Medicine, Philadelphia, Pa., as General Chairman, will be in charge of arrangements, entertainment and the program of Clinics, Panel Discussions, and Clinical-Pathological Conferences.

A.C.P. Research Fellowships in Internal Medicine

The American College of Physicians offers a limited number of fellowships in medicine for the period, July 1, 1954–June 30, 1955. These fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine.

Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from $3,000.00 to $3,500.00; announcements of awards will be made November, 1953.

Application forms, which must be submitted in duplicate not later than October 1, 1953, will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

The James Edgar Paullin Scholarship Fund

Following the death of Dr. James Edgar Paullin, M.A.C.P., friends and associates of Dr. Paullin established the James Edgar Paullin Scholarship Fund at the Emory University School of Medicine, Atlanta, Ga. A recent report from the Chairman of the Committee, Dr. Carter Smith, F.A.C.P., indicates that the capital of the Fund has now increased to $18,653.56, plus several gifts of stock. The Fund is invested and is now earning a sufficient income to more than take care of one $500.00 scholarship, currently being awarded each year. The Committee expresses the hope that the Fund will be eventually increased to $30,000.00 by annual gifts from past contributors and other sources, thus enabling the committee to make awards of two scholarships each year to deserving medical students. Scholarships already awarded have made possible the continuance of a medical education for two deserving young men.

The A. Blaine Brower Traveling Scholarships

An endowment trust in the amount of $10,000 was established by Dr. A. Blaine Brower, F.A.C.P., a Regent of the College, in 1950, under the following conditions:

"The Board of Regents of the American College of Physicians shall establish a traveling or visiting fellowship, which shall be supported from the income from the A. Blaine Brower Fund, the principal to be held intact, thus to perpetuate this fellowship from year to year. The aim of this fellowship shall be to provide an opportunity for a worthy young physician, preferably an Associate of the College, to spend a month, more or less, as a visiting fellow at some institution, or institutions, for observation and postgraduate study. The Committee on Fellowships and Awards of the College can readily facilitate opportunities for this fellowship at outstanding institutions where a month's observation, contact and study would be an exceptional inspiration and a practical source of training. . . .

"The income, approximately $400.00 each, shall be used for payment of the expenses, in whole or in part, of a deserving and promising young physician for attendance for a short period of time for observation and study at an outstanding institution of medical teaching, research or practice, such beneficiaries to be chosen and such institutions to be designated from time to time by the Board of Regents of the College. . . ."

On November 12, 1950, the Board of Regents made an additional appropriation of $10,000 to the A. Blaine Brower Traveling Scholarship Fund, increasing the number of scholarships to two, starting in 1952; both scholarships to be administered under the same plan and regulations.

Application forms for 1954, which should be submitted by Oct. 1, 1953, may be obtained from the American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Coming Examinations by the American Board of Internal Medicine

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 West Main St., Madison, Wis.

Oral Examinations—San Francisco, Calif., Sept. 30, Oct. 1, 2, 1953. These dates supersede the previously scheduled dates of Sept. 28, 29, 30. Chicago, Ill., Nov. 30, Dec. 1, 2, 1953. These dates reflect no change from those originally scheduled.

Industrial Medical Association Announces Future Meetings

The Industrial Medical Association will hold its 1954 Annual Meeting in Chicago, April 24–30, with Headquarters at Hotel Sherman; its 1955 Industrial Health Conference at Buffalo, N. Y., April 23–29.

Second International Congress of Cardiology

The Second International Congress of Cardiology will be held in Washington, D. C., September 12–15, 1954, immediately preceding the Annual Scientific Sessions of the American Heart Association. The Scientific Program lasting for three days will include formal papers, Panel Discussions, Clinical-Pathological Conferences and visits to important medical centers in Washington and Bethesda. The program will be printed in French, Spanish and English. Immediate translation of some of the papers and discussions will be made in three languages.

A series of Post-Congressional visits and conferences to at least 20 of the leading cardiac clinics in different parts of the United States and Canada has been arranged by special committees of local Heart Associations in the various cities.

1954 and 1955 Meetings, Medical Society of the State of New York

The Medical Society of the State of New York will hold its 1954 Session at Hotel Statler, New York City, May 10–14; its 1955 Session at the Hotel Statler, Buffalo, N. Y., May 9–13.

The Third International Congress of Internal Medicine will be held in Stockholm, September 15–18, 1954; President: Professor Nanna Svartz; Secretary General: Professor Anders Kristenson.

Two main subjects will be discussed at the Congress: (1) Hypertension, Pathogenesis and Treatment; (2) Mesenchymal Diseases (Collagenous Diseases); Common Characteristics and Their Nature. A certain number of other subjects will be dealt with by invited speakers.

Address: Third International Congress of Internal Medicine, Karolinska Sjukhuset, Stockholm 60, Sweden.

1954–55 Fulbright Awards

Detailed information on the various programs for university lecturing and postdoctoral research in Europe, the Near East, Japan and Pakistan under the Fulbright Awards, has recently been made available. Application forms, which must be postmarked no later than October 15, 1953 and additional information may be obtained from Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Ave., N. W., Washington 25, D. C.

Office of the Army Surgeon General Announces Postgraduate Short Courses

A series of 10 short postgraduate courses will be conducted by the Army Medical Service during the fiscal year 1953–54. These courses represent an important feature of the in-service training program carried on by the Army Medical Service for Medical Corps Officers. However, they also are open to a certain number of qualified

physicians and surgeons who wish to avail themselves of the excellent facilities of Army hospitals and installations near their homes.

Particularly, the courses are designed to help medical officers in outlying installations keep abreast of recent medical advances, aid them in developing and improving techniques and skills, and serve as a means of developing qualified teachers and instructors for all phases of professional education and training within the Army Medical Service.

Hospitals, medical centers and other installations participating in this feature of the 1953–54 training program will be Brooke Army Medical Center, Fort Sam Houston, Texas; Fitzsimons Army Hospital, Denver, Colorado; Letterman Army Hospital, San Francisco, Calif., and the Armed Forces Institute of Pathology and Walter Reed Army Medical Center, both in Washington, D. C.

The courses and their dates, listed according to the hospital or installation where they will be given, are as follows: Brooke Army Medical Center, Clinical Laboratory Course (March 15–19, 1954); Fitzsimons Army Hospital, Symposium on Pulmonary Diseases (September 21–25, 1953), Clinical Electrocardiography and Recent Advances in Cardiovascular Diseases (November 9–14, 1953); Letterman Army Hospital, Rehabilitation Techniques in Neuromuscular Diseases and Disabilities (April 5–10, 1954); Armed Forces Institute of Pathology, Forensic Pathology (November 2–6, 1953); Pathology of the Oral Regions (March 8–12, 1954); and Walter Reed Army Medical Center, Seminar in Urology (September 7–9, 1953), Symposium on Circulation and Homeostasis (October 5–9, 1953), Symposium on Physical and Mental Health Standards (April 16–17, 1954) and Recent Advances in Medicine and Surgery, including Psychosomatic Aspects of Medicine and Surgery (April 19–30, 1954).

Applications for admission to any course must be submitted at least six weeks prior to the opening date.

In submitting requests for admission to the courses, applicants should indicate: (1) Their name, rank, service number and primary and secondary M.O.S., (2) organization and station, (3) title of course desired, (4) list of all other courses they have attended during the past two years with dates of each, and (5) category and expiration date.

Seventh Connecticut Postgraduate Seminar in Psychiatry and Neurology

The Seventh Connecticut Postgraduate Seminar in Psychiatry and Neurology will begin its courses of lectures on Sept. 30, 1953, and will continue through May 10, 1954.

From Sept. 30 through Dec. 9, sessions in clinical neurology, neuroroentgenology, electroencephalography, neuroanatomy, neurophysiology, neuropathology, and review and demonstrations in neuroanatomy and neuropathology will be held on Mondays and Wednesdays from 3:00 to 9:30 p.m. at Yale University School of Medicine, New Haven.

From Jan. 4 through Mar. 1 (Mondays), from 3:00 to 10:00 p.m. sessions in general psychiatry (psychopathology, clinical psychology, psychiatric syndromes, therapy, psychosomatic medicine, geriatric psychiatry and psychiatry and law) will be held at the Connecticut State Hospital, Middletown.

March 8 through April 12 (Mondays), a course in child psychiatry will be given and April 19 through May 10 (Mondays), there will be a course in pediatric neurology at Yale University School of Medicine, New Haven, from 6:30 to 9:30 p.m.

There are no fees for the above courses.

Copies of the program may be obtained from the Office of the Assistant Dean for Postgraduate Medical Education, Yale University School of Medicine, 333 Cedar St., New Haven, Conn.

Joint Commission on the Accreditation of Hospitals

Report of Meeting, April 19, 1953, at Chicago, Illinois

This regular meeting was attended by a full quorum of representatives of the American Medical Association, American Hospital Association, Canadian Medical Association, American College of Surgeons and American College of Physicians. Drs. LeRoy H. Sloan, William S. Middleton and Alex. M. Burgess, Sr. represented the College of Physicians. In the following summary the actions taken at this meeting are briefly reported.

The Committee on Radiology rendered two reports, in the preparation of which they were aided by advice from the American College of Radiology and by a conference with a representative of that body. One report dealt with the use of fluoroscopes and proper controls as to their operation, as well as adequate records of every patient concerning the amount of exposure to which he has been subjected. The other dealt with the regulation of the application of radium element, its disintegration products and radio-active isotopes, and provided that this work should be supervised by a physician who is certified or equivalently qualified in radiology or therapeutic radiology. It was recommended that such a physician, or an appropriate committee should designate those individuals qualified to apply these substances and that regulations as to its use should be drawn up. It was further stated that ideally a department dealing with these substances should include a physicist to be available for consultation on dosage, safe housing of isotopes, protection of patients and personnel, and the disposal of waste products. This report was adopted.

The report of the Committee on Multiplicity of Medical Meetings was also adopted. It involved principles which can be summarized as follows: The Medical Staff of a hospital is responsible for the quality of medical care; it must be a self-governing body; and its regular meetings must be primarily for the purpose of reviewing the medical care of patients within the hospital and not for the presentation and discussion of scientific papers. Frequent meetings for this type of clinical review are a "must" and cannot be held in conjunction with those of another hospital or with local medical societies. It was recommended that a doctor should not be a member of the active staff of more than two hospitals.

In dealing with neuro-psychiatric hospitals, the recommendations of a Committee which met with representatives of the American Psychiatric Association were approved. These included an agreement which may be summarized by saying that after due consultation between the two collaborating bodies the ratings and certification of each would be accepted by the other—the American Psychiatric Association accepting responsibility for the departments of psychiatry and the Joint Commission for the other departments.

A report on the status of Canadian hospital affairs was given by the representative of the Canadian Hospital Association, and was discussed and accepted by the Commission.

A report from the Committee on General Practice Departments in Hospitals was discussed at length and, with minor changes, approved. With regard to a resolution concerning the Academy of General Practice's Manual on General Practice Departments, action was tabled until such time as the Board of Regents of the American College of Surgeons, the Board of Trustees of the American Medical Association and the Commissioners of the American College of Physicians may review the same and take action.

On recommendations of the Advisory Committee of the Joint Commission, the following regulations were approved:

(1) No hospital shall be resurveyed for an upgrading until at least six months have elapsed, and until a convenient schedule can be arranged for the field representative.

(2) A completely scored point-rating form shall be returned only to those hospitals which receive provisional accreditation. Non-accredited hospitals, as in the past, and fully accredited hospitals will receive a letter of explanation outlining deficiencies noted by the Commission staff.

A list of hospitals classified according to approval, provisional approval and non-approval, as well as a list of hospitals not yet surveyed, was reported in the Minutes and copies sent to the participating members of the Joint Commission.

The next meeting of the Board of Commissioners of the Joint Commission probably will be held in December, 1953.

Life Insurance Medical Research Fund

Research Fellowships and Grants

Applications for awards available July 1, 1954, will be received by the Life Insurance Medical Research Fund as follows: (1) Postdoctoral research fellowships, until October 31, 1953. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Stipends vary from $3,300 to $4,500. (2) Grants to institutions in aid of research on cardiovascular problems, until November 15, 1953. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

Transplantation Bulletin Established

In an attempt to increase the exchange of information in the field of tissue transplantation among investigators in the laboratories and those at the bedside, *Transplantation Bulletin*, a quarterly publication, has recently been established.

Among the functions of this bulletin are the maintenance and publication at least once yearly of a transplantation registry, which will include all practicing physicians and research workers both in the United States and abroad who are interested in transplantation problems. In addition, it will attempt to keep all members of the transplantation registry informed of forthcoming meetings of the professional societies at which there will be presentations dealing with any aspects of transplantation. It will also serve as a medium for rapid and informal exchange of information on problems and progress in the clinics and laboratories both here and abroad. It will not, however, publish formal papers.

Those in the fields of medicine and biology interested in tissue transplantation are requested to submit their names and fields of interest to E. J. Eichwald, M.D., University of Utah College of Medicine, Salt Lake City. A subscription fee of $3.00, to cover the expenses of printing the bulletin and maintenance of the registry and bibliography, will be payable after the first issue of the bulletin, which is expected to appear this month, has been published.

The American Board of Internal Medicine, One West Main Street, Madison 3, Wisconsin, announces that the following candidates were certified in Gastroenterology on April 10, 1953: (7769) Chester Cassel, 1210 Huntington Bldg., Miami, Florida; (6897) Edwin M. Cohn, 4652 Warnock St., N., Philadelphia 40, Pa.; (7523) John

Waller Findley, Jr., San Mateo Clinic, 23 Baldwin Ave., San Mateo, Calif.; (7386) Abraham Irving Friedman, 405 State Street, Hackensack, N. J.; (5127) George Carl Hennig, 240 E. Palisade Ave., Englewood, N. J.; (7915) Thomas L. Murphy, U. S. Naval Hosp., Nat. Naval Medical Center, Bethesda, Md.; (8785) Kemp Plummer, McGuire V. A. Hospital, Richmond, Va.; (2210) H. Marvin Pollard, M.D., 1313 Ann St., Ann Arbor, Mich.; (1767) Paul L. Shallenberger, Guthrie Clinic, Sayre, Pa.; (8585) Burton A. Shatz, U. S. Naval Hosp., Philadelphia, Pa.; (7468) William J. Snape, 573 Stevens St., Camden, N. J.; (6411) William M. Webb, Box 96, Letterman Army Hosp., San Francisco, Cal.

Dr. Robert F. Loeb, A.C.P. Representative on Division of Medical Sciences, National Research Council

Dr. Robert F. Loeb, F.A.C.P., as of July 1, 1953, succeeded Dr. Harold Jeghers, F.A.C.P., as the representative of the American College of Physicians on the Division of Medical Sciences of the National Research Council.

Dr. Ernest H. Falconer, Acting Governor for Northern California and Nevada

Dr. Stacy R. Mettier, F.A.C.P., College Governor for Northern California and Nevada, has been in Europe since April, and Dr. Ernest H. Falconer, F.A.C.P., San Francisco, has been appointed Acting Governor until Dr. Mettier's return. All proposals emanating from Northern California and Nevada should be submitted to Dr. Falconer for final endorsement and transmission to the College Headquarters. Dr. Falconer's address is 384 Post St., San Francisco 8.

Colonel Leedham Appointed Education Division Chief of the Army Medical Corps

Col. Charles L. Leedham, F.A.C.P., has been appointed Chief of the Education and Training Division, Office of the Army Surgeon General, having taken over his duties on June 2, 1953. Col. Leedham started his Army career back in 1929, and during the intervening 24 years of military service has held a number of responsible posts both in the Continental United States and abroad. Principal among his assignments in this country have been those of Chief of the Medical Service School, Barksdale Field, La.; Chief of the Department of Aviation Medicine, School of Aviation Medicine, Randolph Field, Tex.; Chief, Miscellaneous Branch, Professional Service Division, Office of the Army Surgeon General, Washington, D. C.; Surgeon and Hospital Commanding Officer, Camp Campbell, Ky.; Chief of Medical Service, Fort Leavenworth, Kans.; and Chief of Medical Service, Oliver General Hospital, Augusta, Ga. While at the last post he also held the position of Professor of Clinical Medicine at the Medical College of Georgia.

Outside of Continental United States, Col. Leedham served as Surgeon, Fort Armstrong, Hawaii; Commanding Officer of the 48th Evacuation Hospital, which he organized and took to India and Burma; Surgeon of the First Chinese Army, Ramgarh, India; Commanding Officer, 112th Station Hospital, Base Hospital for Calcutta, India; and Chief of Medical Service, Tripler Army Hospital, Hawaii. Prior to coming to the Office of the Army Surgeon General, Col. Leedham spent two years as Medical Consultant with the Far East Command.

Dr. Donald G. Anderson Appointed Dean of the University of Rochester School of Medicine and Dentistry

Dr. Donald G. Anderson, Secretary of the American Medical Association's Council on Medical Education and Hospitals since 1947, and formerly Dean of Boston University School of Medicine, has been appointed Dean of the University of Rochester School of Medicine and Dentistry, beginning with the opening of the 1953–1954 academic year. Dr. Anderson succeeds Dr. George Whipple, who has been Dean since the founding of the School in 1920 and who will continue to serve as Professor of Pathology.

Therapeutics in Internal Medicine

Dr. Franklin A. Kyser, F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School, Chicago, has contributed an autographed copy of the Second Edition of *Therapeutics in Internal Medicine* to the College Library of Publications by Members. This book, edited by Dr. Kyser, has 84 contributors, many of whom are prominent Fellows of the College.

Dr. Walter B. Martin Named A.M.A. President-Elect

Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., was chosen President-Elect by the House of Delegates of the American Medical Association at the 102nd Annual Session in New York on June 4.

Active in the Association for the past 35 years, Dr. Martin has served as a member of the Board of Trustees and House of Delegates, member of the Association's Council on Medical Service, Committee on Legislation and Coordinating Committee for the National Educational Campaign against socialized medicine. In addition, he was Chairman of the Committee for the Study of the National Health Service in Great Britain and is a past President of the Norfolk County Medical Society, the Medical Society of Virginia and the Seaboard Medical Association. A member of the Southern Medical Association, Dr. Martin is also a former Vice President of the Tri-State Medical Association of the Carolinas and Virginia.

Dr. Martin, who has been a Fellow of the College since 1926, was for many years College Governor for Virginia, and from 1946 until the Annual Session in Atlantic City in April, he served as a Regent. In these capacities, he served as Chairman of many important College committees that have exerted a wide influence on College policies.

Dr. Charles F. Martin Honored

Dr. Charles F. Martin, M.A.C.P., Montreal, at the annual meeting of the Canadian Medical Association at Winnipeg, on June 17, received the highest honor of that society, the Starr Award, in recognition of "achievement so outstanding as to serve as an inspiration to the medical profession." The presentation was made by Dr. Walter E. M. Scriver, F.A.C.P., College Governor for Quebec.

Dr. Martin, now 85 years of age, has had a great influence not only on Canadian medicine but also on American medicine. He was Professor of Medicine and Dean of the McGill University Faculty of Medicine for many years. The Montreal Neurological Institute was founded under his guidance, and he had much to do with

the founding of the Royal College of Physicians and Surgeons of Canada. He is also a former President of the Canadian Medical Association.

Dr. Martin exerted a tremendous influence on the American College of Physicians during its reorganization in the middle twenties, and served as its President, 1928–29. The American College of Physicians conferred upon him a Mastership in 1929 and the Alfred Stengel Memorial Award in 1948.

Mr. Loveland Receives Service Certificate

The Medical Society Executives Conference at its Seventh Annual Meeting, New York City, June 1, 1953, issued to Mr. Edward R. Loveland a Certificate in recognition of his more than 25 years as Executive Secretary of the American College of Physicians. Mr. Loveland assumed the appointment on April 1, 1926.

At this Annual Meeting of the Medical Society Executives Conference, he presented a paper entitled, "Medical Society Group Insurance Plans for Health and Accident and for Professional Liability."

Dr. Julius H. Comroe, Sr., F.A.C.P., York, Pa., was honored during late June by the York County Medical Society at a dinner at the Hanover Country Club, to mark the fiftieth year Dr. Comroe has been in the practice of medicine. A testimonial plaque was presented to Dr. Comroe from the Pennsylvania State Medical Society, likewise symbolizing 50 years of faithful and conscientious service in the profession.

Dr. Comroe graduated from the University of Pennsylvania School of Medicine in June, 1903, on his 21st birthday, being the youngest member of a large class. He is credited with making the highest average before the Pennsylvania State Board of Medical Examiners. He did postgraduate work in the chief clinics and institutions of the United States and Canada, and also in England and on the Continent. He held numerous positions of trust in both World Wars. He is a past Vice President and Secretary-Reporter, York County Medical Society; past Vice President, Pennsylvania State Medical Society; Fellow, American Medical Association and American Public Health Association; member, American Museum of Natural History; and has been a Fellow of the American College of Physicians since 1920.

Dr. Ernest H. Falconer, F.A.C.P., San Francisco, was honored at the Spring Convocation of McGill University, Montreal, Can., on May 27, when he was awarded the degree of Doctor of Laws. Emeritus Professor of Medicine and former Chief of the Hematology Division at the University of California School of Medicine, Dr. Falconer received his M.D. degree from McGill University Faculty of Medicine in 1911, and as final prize man for highest standing in his class, was graduated cum laude. He was elected a Fellow of the American College of Physicians in 1929, and in 1936 was appointed Governor for Northern California. Dr. Falconer also served as a member of the Board of Regents from 1947 until 1950, when he was elected First Vice President of the College.

Dr. Russell S. Boles, Sr., F.A.C.P., Philadelphia, has recently been appointed Special Consultant to the National Cancer Institute, United States Public Health Service, Washington, D. C.

Dr. Alexander B. Leeds, F.A.C.P., Albuquerque, N. M., was presented with a Certificate for 50 years of active practice at a meeting of the Bernalillo County

Medical Society last April. Dr. Leeds graduated from Baylor University School of Medicine (Waco, Tex.) in 1902. He is still in active practice, specializing in diagnosis, psychosomatic medicine and endocrinology at the Albuquerque Medical Center. He started practice in Oklahoma when it was an Indian territory and when doctors traveled by horseback and later by horse and buggy.

Dr. Louis N. Katz, F.A.C.P., Chicago, was recently elected President of the Illinois Society for Medical Research.

Dr. Carl V. Moore, F.A.C.P., St. Louis, College Governor for Missouri, was elected President of the American Society for Clinical Investigation at the recent annual meeting in Atlantic City, N. J. At the same time, Dr. Paul B. Beeson, F.A.C.P., Atlanta, was named Vice President.

At its recent annual convention in Los Angeles, the Society of Biological Psychiatry elected Dr. Francis J. Braceland, F.A.C.P., Hartford, Conn., and Dr. Howard D. Fabing (Associate), Cincinnati, Vice Presidents, and Dr. George N. Thompson, F.A.C.P., Los Angeles, Secretary-Treasurer.

Dr. Granville L. Jones, F.A.C.P., Williamsburg, was recently elected a Vice President of the Neuropsychiatric Society of Virginia at the spring meeting held in Richmond.

Dr. Elmer L. Sevringhaus, F.A.C.P., Nutley, N. J., has been made Vice President of the Association of Medical Directors. Dr. Sevringhaus is Medical Director of Hoffman-La Roche, Inc.

The Officers and Executive Committee of the Ohio University Alumni Association at Athens, Ohio, on June 6, 1953, awarded a Certificate of Merit to Dr. James Alexander Lyon, F.A.C.P., Washington, D. C., "In recognition of distinguished attainments in the fields of Internal Medicine and Cardiovascular Diseases which reflect credit upon his Alma Mater and are viewed with satisfaction by his Alumni Association."

Meeting recently in Los Angeles, the Industrial Medical Association named Dr. Robert Collier Page, F.A.C.P., New York City, President-Elect.

Dr. Robert A. Coen (Associate), Portland, Ore., was elected Secretary-Treasurer of the North Pacific Society of Neurology and Psychiatry at the annual meeting held recently in Portland.

Dr. Kenneth E. Appel, F.A.C.P., Philadelphia, and Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, Va., were respectively elected President and Secretary of the American Psychiatric Association at its recent annual meeting in Los Angeles.

Dr. Randall G. Sprague, F.A.C.P., Rochester, Minn., was recently elected President of the American Diabetes Association at the annual meeting in New York City. A diabetic since childhood, Dr. Sprague is Associate Professor of Medicine at the Mayo Foundation and Consulting Physician of the Mayo Clinic.

Dr. William Rottersman (Associate), Topeka, was recently chosen President of the Kansas Psychiatric Society.

The Chicago Society of Internal Medicine has recently elected the following officers: Dr. Richard B. Capps, F.A.C.P., President; Dr. Arthur R. Colwell, Sr., F.A.C.P., Vice President; and Dr. Edwin N. Irons, F.A.C.P., Secretary-Treasurer.

At a meeting of the staff of the Sharon General Hospital, Sharon, Pa., on June 3, 1953, Dr. Clarence C. Campman, F.A.C.P., of West Middlesex, Pa., and Dr. Edward N. Hagin, F.A.C.P., of Sharon, Pa., were awarded each a plaque for continuous and meritorious service extending over a period of the last forty years.

Dr. William John Stapleton, Jr., F.A.C.P., Detroit, was honored at the Wayne University Alumni Reunion recently and received an alumni award "for outstanding service and achievement." Dr. Stapleton, Emeritus Professor of Medical Jurisprudence and Medical History at Wayne University College of Medicine, was formerly Associate Dean of the College for ten years and Acting Dean for two years.

Dr. C. Brewster Brainard, F.A.C.P., West Hartford, Conn., was one of six physicians to be honored at the 161st Annual Meeting of the Connecticut State Medical Society for his active practice of 50 years.

Dr. Virgil P. Sydenstricker, M.A.C.P., Augusta, Ga., has recently been cited for his excellence in teaching at the Medical College of Georgia. The staff of *The Cadaver*, the school newspaper of the Medical College, presented him with a silver cup.

Dr. Julius H. Comroe, Jr., F.A.C.P., Philadelphia, has been appointed to head the first of a series of "Teaching Institutes" sponsored by the Association of American Medical Colleges. The first in the series of Institutes will be held in Atlantic City, N. J., Oct. 19–26, 1953, and will be entitled "The Teaching of Physiology, Biochemistry and Pharmacology." Dr. Eugene M. Landis, F.A.C.P., Boston, will assist Dr. Comroe as Chairman of one of the sub-committees.

Dr. Jacob C. Geiger, F.A.C.P., Health Officer for Oakland, Calif., received the highest degree of the decoration "La Cruz del Sud" on May 25, 1953, from the President of the Republic of Brazil. The citation read, "For distinguished and valuable services rendered to the Government of Brazil and its people in the fields of Public Health, Medicine, and Science."

Alpha Omega Alpha Honorary Medical Society established a new chapter at the University of Oklahoma School of Medicine in ceremonies held on May 1 at the Oklahoma Club, Oklahoma City. Dr. Josiah J. Moore, F.A.C.P., Chicago, national Secretary-Treasurer, presented the keys and certificates; and Dr. William B. Bean, F.A.C.P., Head of the Department of Medicine at the State University of Iowa College of Medicine, gave the installation address on "Caritas Medici." Charter members in the new Alpha Chapter include the following faculty initiates: Dr. Robert H. Bayley, F.A.C.P.; Dr. Lewis J. Moorman, F.A.C.P.; and Dr. Stewart G. Wolf, Jr., F.A.C.P. Dr. Robert H. Riley, F.A.C.P., Baltimore, a member of the Class of 1913, was made an honorary alumnus initiate.

At the annual meeting of the Pennsylvania Trudeau Society, held at Buck Hill Falls on April 9, Dr. Leon H. Collins, Jr., F.A.C.P., Philadelphia, was named President-Elect, and Dr. Archibald C. Cohen, F.A.C.P., Butler, was elected Vice President.

The American Cancer Society bestowed its Fifth Annual Medal Award "for distinguished service in the field of cancer control" on Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, on April 9. Dr. Pendergrass is head of the Department of Radiology at the University of Pennsylvania School of Medicine and is in charge of the cancer research program there.

Dr. Samuel R. Lehrman (Associate), New York City, was elected Secretary-Treasurer of the New York State Hospital Medical Alumni Association at its recent annual meeting.

Dr. William Dock, F.A.C.P., New York City, Professor of Medicine at the State University of New York College of Medicine at New York City, Brooklyn, was the guest of honor at a recent dinner held at the Waldorf-Astoria. A group of his Brooklyn colleagues presented Dr. Dock's portrait to the College and to the Kings County Hospital. Dr. Jean A. Curran, Sr., F.A.C.P., Dean of the College, and Dr. Israel Magelaner, Medical Superintendent of the Hospital, accepted it. Dr. William H. Resnik, F.A.C.P., New Haven, Conn., was the principal speaker, and among the other speakers were Dr. Chester S. Keefer, F.A.C.P., College Regent, and Dr. Samuel A. Levine, F.A.C.P., Boston, and Dr. Tinsley R. Harrison, F.A.C.P., Birmingham, Ala.

Dr. James Asa Shield, F.A.C.P., Richmond, Va., was installed as President of the Tri-State Medical Association of the Carolinas and Virginia at the recent 54th Annual Meeting in Durham, N. C.

The Trudeau School of Tuberculosis ended its four-week course at Trudeau Sanatorium and Saranac Lake, N. Y., on June 27. Forty-five physicians, the largest number to attend the course in its 39-year history, came from eleven states and twelve foreign countries. Included in the latter group were physicians from Pakistan, Thailand, Canada, Japan, China, Germany, Paraguay, India, Brazil, the Philippines, El Salvador, and Turkey.

The faculty was composed of physicians and scientists from the Saranac Lake area and guests from out of town. Among the latter group were the following Fellows of the American College of Physicians: Dr. J. Burns Amberson of New York, Dr. Theodore L. Badger of Boston, Dr. Konrad E. Birkhaug of Albany, N. Y., Dr. W. Edward Chamberlain, Dr. Julius L. Wilson, and Dr. Esmond R. Long of Philadelphia, and Dr. David T. Smith of Durham, N. C.

Local Fellows who participated in the course included: Dr. Frederick Beck of Ray Brook, Dr. Daniel M. Brumfiel and Dr. John N. Hayes of Saranac Lake, Dr. Roger S. Mitchell, Jr., of Trudeau, Dr. James Monroe of Ray Brook, Dr. Edward N. Packard of Saranac Lake, and Dr. Arthur J. Vorwald of Saranac Lake.

Dr. Nathaniel E. Reich, F.A.C.P., Brooklyn, N. Y., was moderator of the panel on "Rehabilitation of the Cardiac Patient for Work" at the recent annual convention of the American College of Chest Physicians in New York City. He also delivered an address on "The Non-diagnostic Electrocardiographic Patterns."

Many members of the College participated in the Second Annual Convention of the American College of Cardiology, held June 7–9 in Washington, D. C. Speakers and their topics included: Dr. Walter S. Priest, F.A.C.P., Chicago, "Who Is a Cardiac?" Dr. Louis F. Bishop, Jr., F.A.C.P., New York, "Analysis of History Taking in Cardiovascular Diseases"; Dr. Benjamin Manchester, F.A.C.P., Washington, "The History and Physical Examination in the Recognition of Heart Disease"; Dr. John B. Schwedel, F.A.C.P., New York, "Roentgenologic Aspects in the Diagnosis of Heart Disease"; Dr. Simon Dack, F.A.C.P., New York, "Differential Diagnosis of Heart Disease in Pregnancy"; Dr. Samuel Blinder, F.A.C.P., New York, "Differential Diagnosis of Anterior Chest Pain"; Dr. Henry I. Russek, F.A.C.P., Staten Island, N. Y., "Clinical Diagnosis of the Syndrome of Bernheim"; Dr. Benjamin M. Gasul, F.A.C.P., Chicago, "Diagnosis of Pulmonary Stenosis with and without Interauricular Septal Defect"; Dr. B. Marvin Hand, F.A.C.P., Philadelphia, "Diagnosis of Neuropsychiatric Complications in Patients Undergoing Cardiac Surgery"; and Dr. Daniel F. Downing (Associate), Philadelphia, "Diagnosis of Congenital Heart Disease."

Among the distinguished guest speakers at the 31st Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society, to be held Sept. 28–Oct. 1, 1953, will be Drs. Joseph B. Kirsner, F.A.C.P., Chicago; Francis D. Murphy, F.A.C.P., Milwaukee; Irvine H. Page, F.A.C.P., Cleveland and Stanley P. Reimann, F.A.C.P., Philadelphia.

Dr. Wesley W. Spink, F.A.C.P., Minneapolis, College Governor for Minnesota, and Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, Mich., were among the out-of-state speakers at the annual meeting of the Cascade County Medical-Surgical Conference, held in Great Falls, Mont., June 22–23.

Dr. W. Paul Holbrook, F.A.C.P., Tucson, Ariz., delivered the annual Ralph Pemberton Memorial Lecture at a recent joint meeting of the Philadelphia Rheumatism Society and the Eastern Pennsylvania Chapter of the Arthritis and Rheumatism Foundation.

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., Immediate Past President of the American Medical Association, was the banquet speaker at the annual meeting of the Wyoming State Medical Society, which convened June 11–13 at Casper Elk's Lodge. Dr. Ferdinand R. Schemm, F.A.C.P., Great Falls, Mont., was among the guest speakers at the scientific session, his topic being "Clinical Management of Acute Myocardial Infarction."

Dr. Maxwell M. Wintrobe, F.A.C.P., Professor of Medicine, University of Utah School of Medicine, Salt Lake City, delivered a series of six postgraduate lectures on diseases of the blood in Toledo, Ohio, June 9–10. The course was sponsored by the Medical Advancement Trust of the Maumee Valley Hospital.

Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, College Governor for Michigan, conducted a seminar on gastro-enterology in Jacksonville, Fla., June 18–20.

Dr. I. Snapper, F.A.C.P., Chicago, recently presented the annual lecture sponsored by Phi Delta Epsilon fraternity at the Medical College of Georgia, Augusta. His topic was "Metabolic Bone Diseases."

Dr. Thomas M. Durant, F.A.C.P., and Dr. Julius L. Wilson, F.A.C.P., Philadelphia, were included on the faculty that presented the 21st Annual Graduate Short Course for Doctors of Medicine, held in Jacksonville, Fla., June 22–27.

Dr. Jerome W. Conn, F.A.C.P., Professor of Medicine, University of Michigan Medical School, Ann Arbor, recently gave the Arthur S. Loevenhart Lecture on "Endocrine Regulation of the Blood Sugar with Particular Reference to Diabetes Mellitus," in Madison, Wis. The lecture was sponsored by Phi Delta Epsilon fraternity of the University of Wisconsin Medical School.

Dr. Franklin G. Ebaugh, F.A.C.P., and Dr. Charley J. Smyth (Associate), Denver, were among the guest speakers at the yearly meeting of the South Dakota State Medical Association, held in Rapid City, June 14–16. Their respective subjects were "Applied Psychiatry in General Practice" and "Rheumatoid Spondylitis—Its Diagnosis and Treatment."

Dr. Louis Krause, F.A.C.P., Baltimore, former College Governor for Maryland, speaking on "Medicine and the Bible," addressed the banquet at the annual postgraduate session sponsored by the Barbour-Randolph-Tucker Medical Society, which was held at the Tygart Valley Country Club, near Elkins, W. Va., June 18. Dr. Louis K. Alpert, F.A.C.P., Washington, D. C., presented a paper on "Collagen Disorders" and Dr. J. Edwin Wood, Jr., F.A.C.P., Charlottesville, discussed "Management of Congestive Heart Failure."

Under the Presidency of Dr. Hans H. Reese, F.A.C.P., Madison, Wis., the American Neurological Association held its annual meeting in Atlantic City, N. J., June 15–17. Speakers and their topics included on the program were: Dr. Roland P. Mackay, F.A.C.P., Chicago, "Philosophy of a Medical School Department of Neurology"; Dr. Adolph L. Sahs, F.A.C.P., Iowa City, "Techniques"; Dr. Henry W. Woltman, F.A.C.P., Rochester, Minn., "Graduate and Postgraduate Training."

Dr. William M. Hitzig, F.A.C.P., New York City, has recently returned from a trip to the Far East that included China, Thailand, Cambodia, Viet-Nam and India. At the University of Malaya Medical School, Dr. Hitzig lectured on "Medicine at the Crossroads" and made rounds at the University's General Hospital.

Dr. Franklin D. Murphy, F.A.C.P., Kansas City, Chancellor of the University of Kansas, was the principal speaker at the recent dedication ceremonies of the Baird Memorial Research Laboratory, an addition to the Lovelace Foundation for Medical Education and Research and the Lovelace Clinic Building, in Albuquerque, N. M. Brig. Gen. Otis O. Benson, Jr., F.A.C.P., Commandant, U.S.A.F. School of Aviation Medicine, Randolph Field, Tex., also spoke at the ceremonies and praised the work done by Dr. W. Randolph Lovelace, II, Director of the Foundation, and Dr. Clayton S. White, Director of Research.

Dr. Lewis E. January, F.A.C.P., Iowa City, was one of the speakers at the annual meeting of the Colorado Medical Alumni Association of the University of Colorado School of Medicine, which met on June 5 at the University of Colorado Medical Center in Denver. He spoke on "Paroxysmal Ventricular Tachycardia Treated with Intravenous Quinidine."

At the annual meeting of the Mississippi State Medical Association, held in Biloxi, May 11–14, under the Presidency of Dr. G. Lamar Arrington, F.A.C.P., Meridian, Dr. Benjamin B. Wells, F.A.C.P., Little Rock, Ark., and Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., were among the guest speakers.

Dr. Herbert S. Gaskill, F.A.C.P., has resigned as Professor of Psychiatry and Director of the Section of Psychiatry, Indiana University School of Medicine, to accept an appointment as Professor of Psychiatry and Chairman of the Department, University of Colorado School of Medicine, Denver, as of June 15, 1953.

Dr. William A. D. Anderson, F.A.C.P., became Chairman of the Department of Pathology at the University of Miami School of Medicine, Coral Gables, Fla., on August 1. In addition, Dr. Anderson will also be Director of the Pathology Laboratories of the Jackson Memorial Hospital in Miami. He was formerly Professor of Pathology at Marquette University School of Medicine, Milwaukee.

Maj. Gen. Edward A. Noyes, (MC), USA, F.A.C.P., former Commanding General of the Brooke Army Medical Center, Fort Sam Houston, Tex., retired April 30 after 38 years of active duty. Before coming to the Brooke Army Medical Center in 1948, Gen. Noyes was Theatre Surgeon in Europe and had been awarded the Legion of Merit during World War II.

Dr. Harold M. Engle (Associate), formerly of Seattle, Wash., has recently been appointed Manager of the Veterans Administration Hospital at Salt Lake City.

Dr. Eddie M. Gordon, Jr., F.A.C.P., has recently been appointed Medical Officer in Charge of the U. S. Public Health Service Hospital (National Leprosarium), Carville, La. Formerly in charge of the U. S. Public Health Service Hospital in Chicago, Dr. Gordon succeeds Dr. Frederick A. Johansen, F.A.C.P., who retired June 1 after 29 years of service at the Leprosarium.

Dr. George E. Pfahler, F.A.C.P., Philadelphia, has given the Philadelphia County Medical Society a gavel made of mastodon ivory found in Alaska. The presentation was made to Dr. Truman G. Schnabel, F.A.C.P., President of the Society, at the 17th Annual Postgraduate Institute dinner on April 29.

Dr. William A. Sodeman, F.A.C.P., became Chairman of the Department of Medicine at the University of Missouri School of Medicine on July 1. He was formerly Chairman of the Department of Tropical Medicine and Public Health at Tulane University of Louisiana School of Medicine, New Orleans.

Dr. Myron D. Miller, F.A.C.P., former Assistant Chief, Division of Hospitals, Public Health Service, as of August 1, became Medical Officer in Charge of the U. S. Public Health Service Hospital at Seattle, Wash.

MINUTES OF THE BOARD OF REGENTS

ATLANTIC CITY, N. J.

APRIL 14, 1953

The second meeting of the Board of Regents, during the 34th Annual Session, was held at Convention Hall, Atlantic City, N. J., Tuesday, April 14, 1953, convening at one o'clock, with President T. Grier Miller presiding, Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

T. Grier Miller	*President*
LeRoy H. Sloan	*President-Elect*
Walter B. Martin	*First Vice President*
Charles F. Moffatt	*Second Vice President*
Paul F. Whitaker	*Third Vice President*
Richard A. Kern	*Secretary-General*
A. B. Brower	
Alex. M. Burgess, Sr.	
Reginald Fitz	
George H. Lathrope	
Cyrus C. Sturgis	
Marion A. Blankenhorn	
Asa L. Lincoln	
Walter L. Palmer	
Wallace M. Yater	
Edward L. Bortz	
Herbert K. Detweiler	
Harold H. Jones, Sr.	
Howard P. Lewis	
Maurice C. Pincoffs	
Charles A. Doan	*Chairman, Board of Governors*
Thomas M. McMillan	*Chairman, Committee on Postgraduate Courses*

Additionally present as a guest was Dr. H. B. Sweetser, Jr., of Minneapolis, who was invited to present the facilities of Minneapolis in connection with its invitation for the 1955 Annual Session of the College. Dr. Sweetser renewed the cordial invitation to the College to come to Minneapolis and discussed its municipal auditorium, the new Mayo Memorial Building at the University of Minnesota, hotels and the College membership in that area who are ready and willing to coöperate in all respects.

Secretary Loveland then presented a brief review of the Minutes of the Regents and Governors meeting of April 12, which, by resolution, was approved.

PRESIDENT MILLER: "I shall first call upon Dr. Maurice C. Pincoffs, Editor, to make his report on the 'Annals of Internal Medicine.' "

DR. MAURICE C. PINCOFFS: "The main matter in connection with the Annals will be reported by the Chairman of the Committee on the Annals of Internal Medicine, and which includes some reorganization of the administrative side of the journal.

"The Annals, in general, has been progressing as to size. It has gained about eight hundred new subscribers since the last time you heard our report. It is getting out more promptly than it was a couple of years ago, and the length of time now that manuscripts have to wait before publication is only about a third of what it was two years ago.

"In regard to the report that is coming from the Committee, I would like to say that while I am very much in favor of this proposed reorganization, so as to provide a body that embraces the functions of both the Associate Editors and of the Committee on the Annals of Internal Medicine, it is not because of lack of appreciation of what our existing Associate Editors do for the Annals, nor lack of appreciation of the work of the Committee on the Annals.

"Through the years the Editor has resorted to both these bodies for advice and counsel—to the Associate Editors largely on purely professional policy matters, and only very occasionally, and he has always been afforded careful and thoughtful advice from them, which he has always appreciated very much. In the same way the various members of the Committee on the Annals, which has been in existence a long time, have always treated the Editor with the greatest consideration and friendliness, and he has profited very much from having this Committee to which to resort.

"The main argument for the proposed change is that the Annals is now one of the important properties of this College; how it is managed and what its future is should probably be a matter of very careful consideration of the Regents. It was felt that a Committee with more definite terms of reference than either the Associate Editors or the Committee on the Annals had and the line of procedure to be followed would be good preparation for the day that must be coming before very long when you have a change of Editors, when you must determine new questions as to whether the Annals is merely to turn in to the treasury $50,000.00 a year, or whether some of that is to be plowed back into new features to make the journal more valuable to subscribers."

PRESIDENT MILLER: "Thank you, Dr. Pincoffs. The Secretary will now present certain communications."

SECRETARY E. R. LOVELAND: "The first communication, in the form of information, is from Major General George E. Armstrong re the Civilian Advisory Committee, reading in part:

> 'As of April 1, 1953, the new Secretary of Defense has dissolved the former Armed Forces Medical Policy Council and has appointed an Assistant for Health Matters, with a six-man civilian Advisory Committee. The former civilians were:
>
> Dr. Melvin Casberg ..... ACS
> Dr. Isidore Ravdin ..... ACS
> Dr. Al Shands ..... ACS
> Dr. James Hollers .... Dentist
>
> 'These have been carried over, but the following have been added:
>
> Dr. William S. Middleton ..... ACP
> Dr. Dwight L. Wilbur ..... ACP
> Dr. Anthony J. J. Rourke ..... AHA.'

"Obviously, General Armstrong believes they are moving in the right direction and recognizing Internal Medicine and the American College of Physicians.

"The second communication was addressed to President Miller and sent by Dr. Edward H. Leveroos, Associate Secretary of the Council on Medical Education and Hospitals of the American Medical Association, to wit:

> 'The Conference Committee on Graduate Training in Medicine wishes to express its appreciation to the College for the valuable contributions which one of your representatives, Dr. LeRoy H. Sloan, has made to the Committee's work during the past two years. Dr. Sloan has given much time and effort to a special

project of the Committee in conducting a pilot study of residency programs in internal medicine in Illinois and has been a key member of the subcommittee responsible for the preliminary screening of new applications.

'The members of the Conference Committee would like to give recognition to Dr. Sloan for his valued participation in these activities through bringing it to the attention of your Board of Regents.'

"The next communication was received in January and is from Dr. William S. Middleton, former Regent and former President of the College, from which I quote in part:

'Within recent months, in private conversations, there have come to me a series of protests of the demands upon full-time teachers by way of the expenditure of time and substance in participation in the scientific sessions of national organizations. While this has not been an exclusive complaint, the mention of the American College of Physicians as a type brings us into the picture.

'Several of the ablest and most popular teachers have indicated the impossibility of the acceptance of invitations by the American College of Physicians and other organizations because of the financial drain. In one or two instances the distances involved and the time of absence from duties have been offered as secondary objections. One of these statements came from a scientist whom I had eagerly sought for the St. Louis meeting of the College.

'The problem is real since Fellows of the College must pay their expenses whereas non-members receive travel expenses.'"

PRESIDENT MILLER: "I think no action is necessary on these communications, unless someone wishes to make some comment regarding Dr. Middleton's suggestion."

DR. CYRUS C. STURGIS: "Mr. President, that matter came up from a member of my department, a full-time man who doesn't receive much salary. What do we do now about non-members as far as travel expenses are concerned?"

SECRETARY LOVELAND: "We pay their expenses for round trip train and pullman fares and their hotel expenses up to $15.00 per day for the day or days on which they appear on the program."

DR. STURGIS: "Why shouldn't we give serious consideration to giving the same allowances to full-time faculty members, whether they are members of the College or not? I do not include part-time men. There certainly would not be very many."

DR. MARION A. BLANKENHORN: "I would like to speak to the same subject. University departmental budgets do not have the wherewithal to permit men to travel as often as I think they ought."

DR. STURGIS: "I would move that members of the College who are full-time members of a medical school faculty, when on the annual program of the College, shall be reimbursed on the same basis as non-members of the College."

DR. ALEX. M. BURGESS: "I second the motion."

PRESIDENT MILLER: "Any discussion?"

DR. LEROY H. SLOAN: "Mr. Chairman, it seems to me before we pass such a motion as that we ought to have the Finance Committee give us an idea of what that can cost. I can see where we can wreck the College financially in about two sessions if we are not very careful. I think we might better refer that to the Finance Committee, or to the Committee that is going to be responsible for next year's program, rather than passing a motion without knowing too much about its cost. If you want to pay the expenses of the full-time men who are, let us say, in the lower echelons, wouldn't it be much better if we select as speakers men that do not feel they need to have their expenses paid, except in those instances where the man has

some particular thing which we are very anxious to hear, in which case special consideration might be given? I think in our program we should stick to members of the College primarily, except in instances where someone outside the College has something of deep and particular interest, in which case his expenses should be paid; but to make a blanket order of this sort, we are going to embarrass the College in pretty short order."

DR. STURGIS: "I don't think so. I believe it will amount to a very small figure. All full-time medical teachers are in the lower echelons."

DR. SLOAN: "It would be better to analyze the program of expenses since we have got a whole year ahead of us and report it back to the next meeting of the Board, rather than to pass it now and find ourselves in hot water, because it would be largely up to me, I think, as to how much money will be spent to get these men to the next meeting—so you would be putting me into a hole."

DR. A. B. BROWER: "A thing like this may be an accumulative thing, and it seems to me rather than to go into it hurriedly, it would be better to refer it to the Finance Committee to go over and to study carefully, in order to determine what the percentages might be and what the ultimate results might be before we rush into this plan for settlement right now."

DR. STURGIS: "I am perfectly willing to do that with the consent of the seconder, so I would like to withdraw the motion and move that we refer this to the Finance Committee for further study and to be reported back in November."

. . . The seconder agreed and the new motion was seconded by Dr. Alex. M. Burgess. . . .

DR. PINCOFFS: "The trouble with that motion is that the incoming President is going to find himself handicapped to some extent in spite of the fact that no one he asks this year will come under that ruling. If we wait until November, most of the program for next year will already be made up. If there have been refusals on the basis of the fact that it costs too much to the individual, they will have already refused in most instances. Then, too, the General Chairman is the man who brings a good many people to the meeting and may incur much of the expense. I would doubt very much if the total expenses involved in the original motion made by Dr. Sturgis would exceed five thousand or six thousand dollars. That is, for full-time young men in this country who would have their expenses paid. I do not think we should be in the least bit parsimonious in trying to get the very best talent for the Annual Sessions."

DR. WALTER L. PALMER: "I am very sympathetic to the problem presented by Dr. Sturgis, because I know that a lot of the younger men do not come to this meeting, being reluctant to give papers for that reason. On the other hand, I am not sure about the wisdom of drawing the line on full-time men. That might cause some difficulties. Aren't there young men on a part-time basis who spend a great deal of time in research and who are hard up for funds that would come across the country to give a paper as well as full-time men?"

DR. STURGIS: "I don't think so."

PRESIDENT MILLER: "The Veterans Administration has to be considered—and the Army and the Navy."

DR. RICHARD A. KERN: "I was going to make confusion a little more confounded by pointing out that the men in the full-time military service are at the same disadvantage, perhaps even greater, because even academic salaries, low as they are, in many instances today are higher than our military pay. In the second place, at no point in either resolution was there an age factor mentioned, yet the discussers have spoken of young men on full-time basis. It is the young man on part-time basis who is even harder up than the man who has a regular pay check coming in, because when he comes to a College meeting his practice stops and his income with it."

DR. PAUL F. WHITAKER: "I would like to add one point regarding the advisability of drawing the line at full-time men. Certain leaders of certain institutions,

for instance, the tuberculosis institutions in our state, are called upon to travel considerably to present papers and make contributions and their salaries are pretty well fixed. That is a factor to them. Therefore, I doubt the wisdom of drawing the line on full-time men, and despite the fine suggestions that Dr. Pincoffs made, I think it would be best to follow the second motion and refer it back to the Finance Committee, even though there may be some handicap for the present year, and then come up with some definite conclusions as to how these expenses can be paid without impairing the finances of the College."

DR. BURGESS: "A full-time employee of the Veterans Administration who is going to present a paper at a scientific meeting and notifies our Division of Education and Research a certain number of days ahead of the time will have his expenses paid, travel and per diem, so it doesn't count for them."

DR. ASA L. LINCOLN: "I think the Committee should be instructed also to prepare, perhaps, two lists—one, the relative cost of full-time men, and, two, the relative cost of paying everybody."

. . . At this point the motion was put and carried. . . .

PRESIDENT MILLER: "Will Dr. Reginald Fitz now present the memorial which he has prepared on Dr. Francis Blake?"

DR. REGINALD FITZ: "Mr. President,

FRANCIS GILMAN BLAKE

"Francis Blake died suddenly on February 1, 1952, in his sixty-fifth year.

"He became a Fellow of the College in 1930; he served as Governor from Connecticut from 1937–39; on March 30 of the latter year he was elected a Regent. He was a member of the Board of Regents for eight years and was then elected Second Vice President.

"During the period of his greatest activity in the College as Regent and Officer, he held many other important positions: especially, he was Professor of Medicine and Dean of the Yale University School of Medicine, and during the Second World War, Chief of the Typhus Commission and President of the Armed Forces Epidemiological Board.

"He came regularly to meetings of the Board of Regents. When he said, 'I believe this a wise policy,' or 'I disapprove of that,' he was always listened to respectfully and often swayed opinion. He was a quiet man, of gentle manner, in no way self-seeking, yet when he chose to speak, he spoke forcefully, positively and thoughtfully.

"He was Chairman of the Committee on Fellowships and Awards for several years and in this capacity he paid meticulous attention to the proper choice of our Research Fellows. How well selected they were under his chairmanship is clearly demonstrated by the subsequent careers of the Research Fellows nominated by his Committee.

"He was interested in all phases of our program for postgraduate education and, indeed, so long ago as 1940 he made a suggestion which still deserves consideration. He thought that small courses, limited to about fifteen Fellows, covering specific subjects and with preassigned reading, might develop into seminar courses that might prove eventually to be of greater educational value than were larger courses in which the teaching, by necessity, was bound to be impersonal and conducted mainly through clinical lectures and demonstrations.

"He was Chairman of a special committee to consider the advisability of establishing a scientific exhibit at each annual session. He persuaded the members of this committee to report to the Regents against such a plan, his reasons for so unfavorable a report well illustrate his conservatism and clarity of thought. The Regents adopted his report and its recommendations and the matter has not been subsequently reopened.

"When a new edition of the history of the College is written, Francis Blake will be described as a particularly distinguished Fellow who during his tenure as Officer and Regent did all that he could to forward our three chief objects. It can truly be said of him that he advanced the highest possible standards in medical education and clinical research, that he perpetuated the best traditions of medicine and medical ethics, and that he maintained the dignity and efficiency of Internal Medicine in its relation to public welfare.

"Mr. President, I move that this be added to the record of the Minutes of this meeting of the Board of Regents."

. . . The motion was seconded by Dr. Alex. M. Burgess, put and carried. . . .

PRESIDENT MILLER: "I wish now to bring up a matter in reference to Dr. Brower's appointment on a Committee for selecting Brower Scholars. At a former meeting, a motion was passed to the effect that Dr. Brower should be permanently on the Committee that selects Brower Scholars. That Committee is the Committee on Fellowships and Awards. The question has arisen as to whether Dr. Brower's participation shall apply only to the selection of the Brower Scholars or whether he is to be a permanent member of the Committee on Fellowships and Awards and take part in all its activities. This matter needs clarification by action of the Regents. I would like Dr. Sturgis to express an opinion about it."

DR. STURGIS: "As I am Chairman of the Committee on Fellowships and Awards, we would be happy to have Dr. Brower participate in all functions of the Committee, but I think his special interest is in the Brower Scholarships. The Committee has many other duties, such as the management of the Latin-American Fellowships, the College Research Fellowships, and various other things that I think are not chiefly his interest. It was my idea that he should permanently participate in the selection of the Brower Scholars, and I think that was the intent of the original motion."

DR. BROWER: "I am quite sure at the time this motion was adopted that its intent was that I should participate only in that part of the program in which the Brower Scholars are selected, and with that intent, I think it should be made definite in the resolution."

. . . On motion by Dr. Cyrus C. Sturgis, seconded by Dr. Paul F. Whitaker, put and carried, it was

RESOLVED, that Dr. A. B. Brower's membership on the Committee on Fellowships and Awards shall have to do only with the Brower Scholarships, and that he not function insofar as the other activities of that Committee are concerned. . . .

PRESIDENT MILLER: "Will Dr. George Morris Piersol, as Chairman of the Committee on Advertising and Technical Exhibits, report now, please?"

DR. GEORGE MORRIS PIERSOL: "Mr. President and Regents: Your Committee has met on several occasions during the past year, has kept in close touch with one another and has passed upon the propriety of all advertisements for the Annals and on exhibits for the annual meeting. Yesterday morning the Committee made a tour of all the exhibits, conferred with various exhibitors and checked to see that their requests and directions had been properly carried out. Our feeling is that the Exhibits are extremely satisfactory, and we have had the coöperation of all the exhibitors.

"Yesterday afternoon at 5:30 we held a meeting of the exhibitors with Officers of the Medical Exhibitors Association in attendance. The group particularly selected consisted of those who control the activities of the exhibiting firms. We discussed with them various problems and gave them an opportunity to present their viewpoints. The meeting was most harmonious and coöperative, and it is the feeling of the Committee that in the last several years both the quality and dignity of the Exhibit have been steadily improved.

"If there is any Regent who feels otherwise and believes certain changes should be made, or feels there is any impropriety about any of these exhibits, the Committee will be glad to have his report. The Committee believes the supervision of these

exhibits is an effort worth while, and we now can truthfully say we have, perhaps, the most select, most appropriate and best Exhibit of any of the medical groups."

PRESIDENT MILLER: "Thank you, Dr. Piersol. May we now have the report of the Committee on Fellowships and Awards, Dr. Cyrus C. Sturgis, Chairman?"

DR. STURGIS: "The Committee on Fellowships and Awards met on Sunday, April 12, in Convention Hall, Atlantic City, N. J., with the following in attendance: Dr. Cyrus C. Sturgis, Chairman, and Dr. Wallace M. Yater, and Dr. E. Hugh Luckey, Director of the Orientation Course at Cornell. Dr. Charles A. Doan and Dr. William C. Menninger were absent.

"The Committee reviewed the 1950 and 1951 group of Latin-American Fellows, all of whom concluded their fellowships earlier this year, with the exception of one to be concluded in June, 1953.

"The Committee then reviewed the 1952 group of Latin-American Fellows who have all been placed under Preceptors. Having just started their programs (most of them as of March 1, 1953), it has not been possible to get progress reports from the Preceptors at this time, but interim reports will be on file by the time of the next meeting of the Committee."

. . . Dr. Sturgis then reviewed in detail the programs of several of the Latin-American Fellows for record in the Minutes. . . .

"In connection with the Research Fellowship Program, we have two delayed cases: (1) Dr. E. Harvey Estes, Jr., whose previous fellowship was interrupted, after working from July 1, 1950, to October 11, 1950, because of active service in the Navy, and (2) Dr. Sidney Harold Ingbar, who was unable to start his fellowship on July 1, 1951, because of call to service. The funds for the above fellowships were held in escrow and both the above will resume their fellowships on July 1, 1953—Dr. Estes under Dr. James V. Warren, Duke University, and will conclude it after 8½ months, or about March 15, 1954. Dr. Ingbar will take up his fellowship for 12 months, under Dr. William B. Castle, Thorndike Memorial Laboratory.

"In the case of the current 1952–53 Research Fellows who are presently at work and whose work will be completed in the next few months, reports will be obtained from their Preceptors at the conclusion of the fellowships and their certificates will be issued at that time.

"At the November 16, 1952, meeting of the Board of Regents, 7 Research Fellowships were awarded; 5 accepted their fellowships, but 2 (Dr. William S. Dingledine and Dr. Gerald H. Whipple) accepted other fellowships and declined the A.C.P. awards.

"The Committee wishes to report that the two 1953 A. Blaine Brower Traveling Scholars have started their programs. Dr. Walter S. Coe has already spent two weeks at Harvard Medical School, where Dr. Eugene C. Eppinger arranged his work. Dr. Coe expresses great satisfaction with the opportunity to learn the organization of the Department of Medicine and the teaching methods employed, and he will report for two additional weeks during October, 1953, to Dr. Francis C. Wood, Professor of Medicine at the University of Pennsylvania School of Medicine to complete his work. The other Brower Scholar, Dr. John H. Woodbridge, spent March 15, 1953, to April 11, 1953, with Dr. Jerome Conn, University of Michigan Medical School, in the field of diabetes mellitus.

"The Committee again would like approval from the Board of Regents to conduct a meeting of the Committee on Fellowships and Awards in Ann Arbor during June, 1953; a similar meeting was held last year on June 21. It is at that time that we receive the applications from the Kellogg Foundation."

. . . On motion by Dr. Cyrus C. Sturgis, seconded by Dr. Walter L. Palmer, put and carried, the report was accepted and the meeting of the Committee at Ann Arbor in June, 1953, was authorized. . . .

DR. FITZ: "May I ask why two Research Fellows refused their fellowships?"

DR. STURGIS: "They made multiple applications, and they took the one that paid the most. We raised our stipends a year or so ago, but there are some that pay even more. Occasionally an applicant may accept the fellowship that is offered to him first. Multiple applications are often made because they want to be as sure as possible of getting a fellowship."

PRESIDENT MILLER: "Next is the report of the Committee on Educational Policy. Dr. Marion A. Blankenhorn, Chairman."

DR. BLANKENHORN: "The Committee on Educational Policy met at Convention Hall, Atlantic City, N. J., at 10:00 A.M., April 13, 1953, with the following in attendance: Dr. Marion A. Blankenhorn, Chairman, Dr. Edward L. Bortz, Dr. Harold H. Jones, Sr., Dr. Maurice C. Pincoffs and Dr. Cyrus C. Sturgis.

"The first matter for consideration was the review of the resolution adopted by the Board of Regents on November 16, 1952, as follows:

> 'RESOLVED, that the Committee on Educational Policy be enlarged to five in number; that the Committee be relieved of duty with the Committee on Postgraduate Courses and be instructed to undertake, with the aid of the Executive Secretary, a systematic collection of the evidences of membership satisfaction or dissatisfaction with the program at the Annual Session; that the Committee study these evidences by special meeting, if need be, and submit a report as promptly as possible to the Consulting Committee on Annual Sessions.'

"A specimen questionnaire has been suggested by Dr. Pincoffs and the Chairman, and revised by Mr. Loveland. This questionnaire is now in the hands of the Regents for their consideration. It was decided by the Committee to use the questionnaire to study the present Session of the College. The questionnaire is to be put into the hands of the Governors by the Chairman of this Committee, with the request that each Governor and five members selected by each Governor are to report on the questionnaire, sending same back to Mr. Loveland. Mr. Loveland is requested to tabulate the results of the questionnaire for the guidance of the Committee on Educational Policy and for the Consulting Committee on Annual Sessions.

"The Committee discussed the educational functions of the College, which were never clearly defined to them. It is agreed that educational functions of the College are to teach Internal Medicine to its members. Various techniques of teaching were explored, especially newer techniques in television. Dr. Bortz and Dr. Sturgis are experimenting in television in their own institutions, and they have agreed to bring progress reports to the next meeting of this Committee.

"The Committee made no decision about distributing this questionnaire, or a similar questionnaire to the entire membership, by including it in the printed Program. The decision to distribute it to the entire membership must rest with the Regents. The Committee makes no formal recommendation on that point.

"We briefly considered the matter submitted by President-Elect LeRoy H. Sloan, which has to do with the Council for Financial Aid to Education, Inc. Your Committee has nothing to recommend."

PRESIDENT MILLER: "Any comments on this report?"

DR. HOWARD P. LEWIS: "I think this questionnaire is a very good idea, and I would like to move that this be included in the printed Program of next year, and circulated thereby to all the people who attend the Session, so as to get a good overall coverage. It could be a loose-leaf or perforated form placed in the Program for next year's Annual Session."

. . . There followed extended discussion about the questionnaire and whether it should be immediately released at this Session to all the members in attendance, with the request to fill it out and drop it in a ballot box, or to give the opportunity to the Committee to proceed as they suggested, with a sampling through the various

Governors. Dr. Sloan, in particular, favored the release of the questionnaire to all members present at this Session, so that the opinions could be promptly tabulated and used immediately. Others felt that a sampling of perhaps three hundred members would be just as effective as distributing the questionnaire to every one, and still others felt the general membership would like to have an opportunity to express their opinions. . . .

. . . Dr. Howard P. Lewis and the seconder withdrew their motions, and Dr. Walter L. Palmer was requested to state a new motion. . . .

DR. PALMER: "I move that the matter of the publication of this questionnaire, or a similar one, with the program for next year or in the Annals or a separate distribution to the membership of the College be referred to the Committee on Educational Policy, with the expectation that it will report its recommendations at the November, 1953, meeting of the Regents."

. . . The motion was seconded by Dr. Alex. M. Burgess, put and carried; however with a "Nay" recorded by Dr. LeRoy H. Sloan. . . .

DR. BURGESS: "I move that the original recommendation of the Committee to the effect that this questionnaire as already prepared be referred to the Governors as recommended by the Committee on Educational Policy."

. . . The motion was seconded by Dr. Cyrus C. Sturgis, put and carried. . . .

PRESIDENT MILLER: "Dr. Thomas M. McMillan, Chairman, will report for the Committee on Postgraduate Courses."

DR. THOMAS M. MCMILLAN: "Gentlemen, since our last report to the Regents, we have completed the autumn 1952 series of courses and are now just half through the spring series of courses. It is interesting to observe that the registration seems to maintain the same level. For the calendar year 1952 there were 1,101 registrants for these courses, about the same number that we have had successively year after year since World War II. I think it is true to say that the registration for most postgraduate teaching has declined, and the fact that ours is stationary is quite good.

"We have attempted to uncover new directors and new institutions to be represented on our schedule, and we have been fairly successful. In the autumn series for 1952 we had three new directors who had never directed courses for us, and all of them did excellent jobs. In the 1953 spring series we have one new director.

"Incidentally, many institutions apply to us to give courses now, whereas at the very beginning of our program several years ago some institutions were reluctant to join our program.

"At this time we would simply like to ask the Regents to approve the following schedule of courses for 1953:

"(1) CARDIOVASCULAR DISEASES
New York University College of Medicine; Charles E. Kossmann, M.D., F.A.C.P., Director; October 12–17, 1953.

"(2) PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE
Duke University School of Medicine; Eugene A. Stead, Jr., M.D., F.A.C.P., Director; October 12–16, 1953.

"(3) INTERNAL MEDICINE
University of Chicago School of Medicine; Wright R. Adams, M.D., F.A.C.P., Director; October 19–23, 1953.

"(4) CLINICAL NEUROLOGY
Jefferson Medical College of Philadelphia; Bernard J. Alpers, M.D., F.A.C.P., Director; November 2–6, 1953.

"(5) PRESENT DAY THERAPY AND ITS PHYSIOLOGIC BASIS
University of Utah College of Medicine; Maxwell M. Wintrobe, M.D., F.A.C.P., Director; November 9–13, 1953.

"(6) SEMINARS IN INTERNAL MEDICINE
Vanderbilt University School of Medicine; Rudolph H. Kampmeier, M.D., F.A.C.P., and Hugh J. Morgan, M.D., F.A.C.P., Co-Directors; November 16–20, 1953.

"(7) THE NEWER BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO CLINICAL PROBLEMS.
University of Wisconsin Medical School; William S. Middleton, M.D., M.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Co-Directors; November 16–20, 1953.

"(8) BALLISTOCARDIOGRAPHY
Johns Hopkins Hospital; Benjamin M. Baker, M.D., F.A.C.P., Director; three days.

"This last course is a tentative suggestion. The Committee has been concerned with the possibilities of three-day courses, but feels it should not use them except for subjects the content of which lends itself better to three days of presentation than to five days. We have received a number of requests for a course in Ballistocardiography, the newest of the graphic methods for studying the heart. Some might think that the subject is not ready for teaching or presentation, but in talking with many who had thought this matter through, they believe such a course would be justified at this time, because it might save a good deal of confusion that exists and would at least tend toward the adoption of some sort of uniform classification of terminology.

"For the spring of 1954 we would like to get your approval for the following partial schedule:

"(1) CLINICAL GASTRO-ENTEROLOGY
Louisiana State University School of Medicine; G. Gordon McHardy, M.D., F.A.C.P., Director.

"(2) ALLERGY
University of Pittsburgh School of Medicine; Leo H. Criep, M.D., F.A.C.P., Director.

"(3) ELECTROCARDIOGRAPHY
Wayne University College of Medicine; Gordon B. Myers, M.D., F.A.C.P., Director.

"(4) HEMATOLOGY
Chicago Institutions; Howard L. Alt, M.D., F.A.C.P., Leon O. Jacobson, M.D., F.A.C.P., and Louis R. Limarzi, M.D., F.A.C.P., Co-Directors.

"(5) INTERNAL MEDICINE
Columbia University College of Physicians and Surgeons; Franklin M. Hanger, M.D., F.A.C.P., Director.

"(6) INTERNAL MEDICINE
Temple University School of Medicine; Thomas M. Durant, M.D., F.A.C.P., Director.

"(7) NEOPLASTIC DISEASES AND RADIOISOTOPES
Memorial Center for the Treatment of Cancer and Allied Diseases; Cornelius P. Rhoads, M.D., F.A.C.P., and Rulon Rawson, M.D., Co-Directors.

"Among new directors the Committee has in mind for other courses are Dr. Herrman L. Blumgart, Boston, Dr. Eugene Ferris, Atlanta, Dr. Paul Beeson, New Haven, Dr. Walter S. Burrage, Boston, and Dr. John S. Lawrence, of Los Angeles. Still another possibility suggested to us is a course in Isotopes by Dr. William G. Myers, of Columbus.

"Gentlemen, these are the courses that we have in mind and these the new directors we have under consideration. Not in all cases are we sure when we shall use them."

. . . On motion by Dr. Wallace M. Yater, seconded by Dr. Alex. M. Burgess, put and carried, the proposed schedule of courses was approved. . . .

PRESIDENT MILLER: "The next report is that of the Committee on Public Relations by Dr. Edward L. Bortz, Chairman."

DR. EDWARD L. BORTZ: "Mr. President, first, we had a number of communications referred to this Committee:

"(1) A pamphlet entitled 'Let the Patient Beware,' a pronouncement about a case in court concerning an osteopath, 'a patient who seeks treatment from an osteopath for the cure or alleviation of his condition is charged with knowledge of the fact that the osteopath would follow the methods and practices observed in the osteopathic system of treatment, and is not in a position to complain that the methods and standards of practice customarily observed by another school of medicine were not followed.'

"This is an item about the so-called double standard of the practice of medicine; damage suit was instituted in the Michigan Supreme Court. An extract from the proceedings indicates 'An osteopathic surgeon has the duty to use that degree of care and skill in the handling of a thyroid condition in a patient, and in the treatment given the patient, that is customarily used in the community or similar communities by ordinary or average practitioners of osteopathy and is not held to the observance of standards of practice or methods of practice customarily observed by practitioners belonging to other schools devoted to the cure, alleviation and treatment of human ailments and diseases.'

"Obviously, there is no action called for.

"(2) A letter from Dr. Julien E. Benjamin, F.A.C.P., with regard to the flow of medical news to the public. There is a point here that the Committee thinks the Board of Regents should act on. Quoting from Dr. Benjamin's letter to the Executive Secretary:

> 'There seems to be an unhealthy competitive effort on the part of reporters and specialty writers to rush into print items pertaining to medical discoveries and "new cures," to the detriment of the unsuspecting public. Particular reference is made to subjects of cancer and poliomyelitis, matters of vital concern to every intelligent person. Several other serious diseases, whose causes and cures are far from settled, fall into this category.
>
> 'In addition to giving false hope to sufferers, premature publicity serves to confuse the public and in the end endangers the confidence the layman has vested in the medical profession. The effect of these false hopes on the morale of individuals who have serious illnesses has been pitiful in some instances. The resentment and criticism by many readers not only of the newspapers for premature reporting, but also of the doctors for not exercising some control has been considerable.
>
> 'Would it not be a good plan for the "College" to appoint a strong committee (or possibly one already existing) to call a meeting of the several news services and together agree on a sensible pattern for release of important medical discoveries and advances in medical knowledge to the public?
>
> 'Another feature inherent in the overall picture has been the use of doctors' names, their locations and the hospitals from which their work emanates. This type of publicity is justified only in unusual instances, where epochal advances in medical knowledge have been substantiated reliably and cleared by head of departments, institutions, or officially appointed groups.'

"The Committee weighed the recommendation of Dr. Benjamin with reference to the College appointing a strong committee to call a meeting of the several news services and together to agree on a sensible pattern for release of important medical discoveries and advances in medical knowledge to the public. We think the letter should be answered and that it be called to Dr. Benjamin's attention that the College is already doing what it can through its own channels of release of information from the Annual Sessions; also a letter should be written to the American Medical Association, suggesting that they take action on it and I so move."

. . . Seconded by Dr. Howard P. Lewis, put and carried. . . .

DR. BORTZ (continuing):

"(3) A letter from Dr. Arthur B. Richter, F.A.C.P., regarding the A.C.P. representation on governing bodies of Blue Cross and Blue Shield.

"It is an important communication, because there is no doubt that there is a differential in fees paid by the Blue Shield to surgeons and internists, with the result that internists receive inadequate consideration in cases of emergency and where highly specialized knowledge and experience are required. Dr. Richter said in part, 'It appears to me that the entire setup for hospital and health insurance is controlled, so far as the medical profession is concerned, by the surgeons. I think it is time that the American College of Physicians asserts itself in this respect. . . . We internists do a lot of griping about the surgical fees, and I was just interested in what the American College of Physicians has done with respect to hospital and medical insurance.' I wonder if Dr. Sloan would comment on this?"

DR. SLOAN: "I think it is important and I don't think that the College is correct in passing the problem up by simply stating that we are not interested in anything economic or political. We are interested in the internist, and we are having constant inquiries concerning this particular problem. . . .

"The problem of the fee of the internist in practice, away from educational and institutional practice, is becoming increasingly marked, and unless we do something about it, trouble is sure to arise. If you, as an internist, see a patient who has had an appendectomy and develops pulmonary embolism, you can receive no fee as an internist from Blue Shield, and if the surgeon pays you a fee, you are fee-splitting. Therefore, you are on very insecure grounds at present. I recommend, Mr. President, this communication be referred to the proper offices of the American Medical Association for their consideration, since they are the mother body of all of us, and that our Officers be empowered quietly to consult with Blue Shield along those lines, and I so move."

. . . The motion was seconded by Dr. Herbert K. Detweiler, and opened for discussion. . . .

DR. WALTER B. MARTIN: "Undoubtedly there is a problem. The College isn't the one to solve it. It is not correct to say that the internist doesn't get anything, but under most of the Blue Shield plans, the surgeon would get his regular operating fee and the internist gets a consultation fee of $10.00, even though he cared for the patient for three weeks. I think this ought to go to the Section on Internal Medicine of the American Medical Association, to be considered by them and then referred to the proper body of the American Medical Association as to what shall be done."

. . . Dr. LeRoy H. Sloan's motion was put and carried. . . .

. . . On recommendation of the Committee on Public Relations a case involving claims of plagiarism against a member of the College by another physician, after having been thoroughly investigated, was dismissed as having no basis of fact. Also, on the recommendations of the Committee, the dues of four members were waived from January 1, 1953, because of disablement and/or retirement from active practice.

Also, the resignations of

Dr. Francis N. Dougherty (Associate), Pottsville, Pa.
Dr. Ralph Lynch, F.A.C.P., Pittsburgh, Pa.
Dr. Margaret R. Reynolds, F.A.C.P., Peterborough, N. H.

were accepted. One Fellow was dropped from the Roster, in accordance with provisions of the By-Laws, because of delinquency in dues of more than two years' standing. . . .

PRESIDENT MILLER: "Now, the report of the Committee on the Annals of Internal Medicine by Dr. Alex. M. Burgess, Sr., Chairman."

DR. BURGESS: "Your Committee met on Monday, April 13, 1953, during the 34th Annual Session at Atlantic City, N. J. There were present Doctors Walter L. Palmer, Howard P. Lewis and Alex. M. Burgess, Sr., Chairman. The Editor, Dr. Maurice C. Pincoffs, attended the meeting, as did also Mr. E. R. Loveland, Executive Secretary of the College.

"1. *Circulation and Finances:*
The circulation of the Annals continues to increase each year, as does the net profit. Attached to this report is the agenda for the Committee meeting, which contains a statement of the facts. They may be summarized by saying (1) that the circulation as of March, 1953, was 16,307, as compared with an average of 15,783 in 1952, and (2) that the profit on Volumes 35 and 36 was $67,718.37, as compared with $58,014.61 for the previous year, an increase of $9,703.76. It is perhaps worth mentioning that this increase is almost enough to cover the cost of using the better grade of paper, a matter which is discussed below in Paragraph 2, (c).

"2. *Physical Changes in the Annals:*
Your Committee has given further consideration to the matter of changes in the format of the Annals and in the quality of paper used. It has had the benefit of a study made by the Butler Typo-Design Research Center, experts on typography and format. It appears obvious to your Committee that these consultants are unfamiliar with the objectives and requirements of a scientific publication. Most of the recommendations appear to have as an objective 'reader appeal' and to be applicable for the most part to popular magazines.

"(a) Certain changes should be given consideration and have been discussed in previous reports. In talking about the matter with a number of Fellows of the College, the members of the Committee gained the idea that the publication of the contents on the outside cover is popular. That this feature should be retained is the opinion of the Committee.

"(b) At the meeting of the Board of Regents on April 25, 1952, samples of various types of cover were exhibited and the one designated as 'No. 1,' which was light green in color, with the Seal of the College shown in gold and the contents on the front cover. After careful consideration of all factors concerned, and in view of the fact that the Editor is not in favor of a color change, the Committee has decided to recommend merely a slight change in the type on the front cover, which will increase the clearness and readability, but will not be a noticeable alteration of the appearance of the journal.

"At this point it may be appropriate to call attention to the fact that the Annals has been developed from a small, struggling publication, when the present Editor

took over, to the leading journal that it now is, by the efforts of our Editor, backed by Mr. Loveland's office. Under these circumstances, it is quite understandable that your Committee is loath to urge anything to which our Editor feels strongly opposed.

"(c) Regarding the use of a heavier, coated paper stock, your Committee, having made comparisons of halftone reproductions of the same x-ray film on different grades of paper, is of the opinion that a stock that is somewhat heavier and coated should be used. Comparison of various samples leads us to the belief that a paper of approximately the grade of the 60 lb. stock which we examined should be used. Although this will mean an increase in costs of over $10,000.00 a year, we believe that the profit now being earned by the Annals amply justifies this improvement.

"(d) The use of two columns to the page. This has been recommended by several people to your Committee. There are some considerations, such as an alleged improvement in ease of reading and possibly some economy of space, which recommended this change, but your Committee does not feel that this is a very important matter and recommends that it be considered by the Editor, to be decided as he sees fit.

"3. *Administrative Reorganization:*
In previous reports of this Committee the suggestions of the Editor as to the appointment of an Editorial Board to function in the place of this Committee and of the Associate Editors, have been mentioned. Now there is presented (attachment No. 2) a communication from the Editor which is a clear statement of a reorganization along these lines.

(Read "Proposed Administrative Organization of the Annals of Internal Medicine" at this point.)

Your Committee gives its full support to this proposal.

"4. *Increase in the Advertising Rates:*
The Executive Secretary has pointed out to this Committee that the present advertising rates of the Annals are low and should be increased. He submits an amended schedule of rates which represents an increase of approximately 16%. In view of the rise in printing costs and the higher rates charged by other journals, your Committee believes that the increase proposed by Mr. Loveland is justified.

"5. Attention was called in the report of this Committee presented on November 18, 1951, to *delays in the publication of articles* after submission to the Annals and of some delay in editorial decision as to acceptance or rejection of articles submitted. There are presented herewith figures prepared by the Editor, which show that these delays have now been eliminated. The figures as to the number of manuscripts accepted and rejected for the past three years are also presented.

"*RECOMMENDATIONS:*

"1. Regarding the *format* of the Annals, it is recommended:

"(a) That such minor changes in the type on the cover of the Annals as have been discussed with the Committee be considered by the Editor and Executive Secretary, with power to act.

"(b) That the matter of two columns per page be considered further by the Editor.

"(c) That a heavier and coated paper stock, of approximately 60 lb. quality, be used in the Annals, the choice of the exact paper and the time when the change should be made being left to the judgment of the Editor with the advice of the Executive Secretary.

"2. That the *plan of reorganization* proposed by the Editor and involving the abolition of this Committee and of the group of Associate Editors, and the establishment of an Editorial Board, as described in the communication received from the Editor, be adopted forthwith.

"3. That the Executive Secretary be authorized to *increase the advertising rates* as recommended by him.

"4. That the *Board of Regents express to the Editor* at this time, *and to the Executive Secretary, its deep appreciation* of what they have done to make the Annals the outstanding journal in its field, which it now is.

Respectfully submitted,
Walter L. Palmer
Howard P. Lewis
Alex. M. Burgess, Sr., Chairman."

. . . A motion was made by Dr. Paul F. Whitaker, seconded by Dr. Edward L. Bortz, to adopt the recommendations of the Committee, and the motion was opened for discussion. . . .

DR. FITZ: "May I ask why the proposed reorganization and setup is deemed wise? It is not very different from what we now have."

DR. BURGESS: "The plan proposed gives continuity to a group that will handle the affairs, rather than continuing a small committee. It is a group that the Editor can use both as consulting editors and in connection with all policy and administrative problems. It does not have a separate group of Associate Editors whose names appear on the back page of the journal, but who really do not do very much. It gives the Editor one group appointed by the Regents, responsible to the Regents, on which he can depend at all times for all kinds of assistance. Dr. Pincoffs worked this plan out himself, and he persuaded us that it is good, and I think it is."

DR. PALMER: "It is my recollection that Dr. Pincoffs had in mind that the Editor should report annually to this Editorial Board and that the Editorial Board should report annually to the Regents. The Regents still retain authority."

. . . The motion was put and carried. . . .

PRESIDENT MILLER: "May we now have the report of the Committee on Finance, Dr. A. B. Brower, Chairman?"

DR. BROWER: "Mr. President and members of the Board of Regents: The Committee on Finance met on Sunday, April 12, at Convention Hall, Atlantic City, N. J., with Dr. William D. Stroud, Treasurer, and Mr. E. R. Loveland, Executive Secretary, sitting in. You have received a duplicated copy of the Financial Statements and the Auditor's Report for 1952. The Committee has reviewed this report and feels it is in good order. All accounts were audited by a Certified Public Accountant. Increase in Funds is indicated as follows:

	Balance Jan. 1, 1952	*Balance Dec. 31, 1952*	*Increase*
Endowment Fund	$347,079.60	$382,598.64	$ 35,519.04
James D. Bruce Fund	10,000.00	10,000.00	
A. Blaine Brower Fund	20,000.00	20,000.00	
General Fund	508,144.00	576,555.52	68,411.52
	$885,223.60	$989,154.16	$103,930.56

"The gross assets of the College amount to $989,154.16.

"Life Membership Fees for 1952 amounted to $25,833.60 (1951, $16,385.00; 1950, $17,561.67).

"Profit on Endowment Fund Security Transactions was $3,135.44.

"Comparison of General Fund Data for the past three years is as follows:

	1952	*1951*	*1950*
Total Income	$350,193.29	$338,270.18	$298,982.55
Total Expenses	257,315.77	222,484.43	205,649.61
	$ 92,877.52	$115,785.75	$ 93,332.94

"Comparison of some of the most important accounts for the past three years is as follows:

	1952	*1951*	*1950*
Annual Dues	$ 52,741.41	$ 51,495.44	$ 44,838.85
Initiation Fees	17,950.00	20,875.00	23,065.00
"Annals," Subscriptions	131,920.26	127,304.08	125,629.57
"Annals," Advertising	56,780.85	58,936.88	31,809.07
"Annals," Expenses	121,050.47	120,867.60	98,851.60
Annual Session, Net Cost	1,492.82	5,655.84*	464.89
Total Income, General Fund	350,193.29	338,270.18	298,982.55
Total Expenses, General Fund	257,315.77	222,484.43	205,649.61
Net Income, General Fund	92,877.52	115,785.75	93,332.94

* Net profit.

"The Committee reviewed all security transactions that have taken place since the last meeting of the Board of Regents and submits for record and approval by the Regents the following: (Read lists of purchases for the Endowment Fund and for the General Fund, and list of recommendations of the Investment Counselors for purchase through available surplus funds, all of which were approved by formal action of the Board of Regents).

DR. BROWER (continuing): "We believe you will be interested in knowing something about the current distribution of securities and present the following analysis:

"Bonds	40.5%	U. S. Government	18.6%
Preferred Stocks	12.0%	Railroad	14.5%
Common Stocks	46.1%	Public Utility	24.0%
		Industrial	28.8%
	98.6%	Bank	12.7%
Uninvested Cash	1.4%	Uninvested Cash	1.4%
	100.0%		100.0%

"The Committee reviewed the wisdom and requirements for new Addressograph equipment in the Headquarters of the College and approve the recommendations of the Executive Secretary. We suggest that an appropriation of $3,000.00 be made to cover this installation."

. . . On motion by Dr. A. B. Brower, seconded by Dr. Howard P. Lewis, put and carried, the appropriation of $3,000.00 was added to the Executive Secretary's budget. . . .

DR. BROWER (continuing): "The Committee also considered a proposal to air condition the General Offices, and recommends same to the favorable consideration of the Regents. This would require an appropriation of approximately $2,800.00.

The Committee suggests this appropriation be made and that the final decision on the unit and its installation be subject to the approval of the House Committee, and I so move."

. . . The motion was seconded by Dr. Herbert K. Detweiler, put and carried. Also, on motion by Dr. A. B. Brower, seconded by Dr. Edward L. Bortz, put and carried, the report of the Committee on Finance was approved as a whole. . . .

PRESIDENT MILLER: "Next, I will call for the report of the American Board of Internal Medicine by Dr. Walter L. Palmer, Chairman."

DR. PALMER: "Mr. Chairman, the total number of Diplomates certified by the American Board of Internal Medicine, as of a week ago, is 8,035. The Board is still holding one written examination per year each October. The number of candidates and the percentage of failures remain about the same. The Board also holds five oral examinations a year in various parts of the country. These have come to be in essence regional examinations, although, for the most part, they are attended by all members of the Board."

PRESIDENT MILLER: "Dr. Palmer, as Chairman, has presented five nominees, one of whom shall be the successor on the Board of Dr. William B. Porter, who is an A.C.P. representative and who is not eligible for reëlection on July 1, 1953. (Read slate of five names as nominees to the American Board of Internal Medicine.)

. . . On motion by Dr. Walter L. Palmer, seconded by Dr. Alex. M. Burgess, put and carried, it was RESOLVED to submit these names with the approval of the Regents to the American Board of Internal Medicine, with the understanding that one would be selected to succeed Dr. William B. Porter for a term of three years, starting July 1, 1953. . . .

PRESIDENT MILLER: "Dr. Sloan, do you have a report for the Conference Committee on Graduate Training in Medicine?"

DR. SLOAN: "On December 17, 1939, the Board of Regents of the College adopted a resolution providing that the Regents should adopt a proposal for the establishment of a Conference Committee on Graduate Training in Medicine, and that the President should appoint two members to represent the College. Doctors Hugh J. Morgan and O. H. Perry Pepper were the first appointees representing the College. During the last War the work of this Committee was largely taken over by the Council on Medical Education and Hospitals and the American Board of Internal Medicine. Doctors Reginald Fitz and Ernest E. Irons worked long and hard on applications submitted for approval of the hospitals of the country for residency training in internal medicine. Following the War, chiefly as the result of the earnest efforts of Dr. Reginald Fitz, the Conference Committee was reactivated in 1946. This Committee is made up of two members from the American College of Physicians, two from the American Board of Internal Medicine and two from the Council on Medical Education and Hospitals of the American Medical Association. Dr. Howard Wakefield, one of the College representatives, was unanimously elected Chairman of this Conference Committee at its last meeting.

"Since the last Annual Session of the College this Committee met on June 9, 1952, and on February 7, 1953. The meeting on June 9, 1952, was saddened by the absence of Dr. Russell L. Haden, who had closed his earthly sojourn while giving a clinic during our Cleveland Session. That meeting was given over to the approval of a specific list of hospitals, to the disapproval of a list of hospitals and to a discussion of a confidential pilot survey of the States of Illinois and Iowa. This survey gave an overall general picture of residencies in these States, but did not permit of specific information sufficient to approve or deny any hospital full approval. It was voted at that meeting to carry out a pilot survey of hospitals giving residency training in internal medicine in the State of Michigan. My illness prevented this effort. At this meeting it was suggested and voted that the requirements for resi-

dency training in internal medicine be reëvaluated. This work has not yet been carried out.

"The second meeting of the Committee, Chicago, February 7, 1953, had in attendance Doctors Howard Wakefield and S. Howard Armstrong for the College; Doctors Walter L. Palmer and Thomas M. Durant for the American Board, and Doctors Charles Stone and Edward H. Leveroos for the Council on Medical Education and Hospitals. Also present were Doctors Henry M. Thomas, Jr. and Victor Logan of the American Board and Mr. Warren von Ehren of the American Medical Association. Dr. Wakefield was elected Chairman. As stated by Dr. Leveroos, the primary function of the Committee is to evaluate the residency training in internal medicine, both in quality and time (period), including new applications and the reevaluation of approved programs, and to establish standards. Shall the program of a given hospital be approved for one, two or for three years? Applicants are led to believe that one hospital is as good as another. The period is not stated in publications, and the specific work of the hospital, such as fellowships, research, etc., is not noted. The period of approval of training has been under discussion for almost fourteen years (1940). As a practical example, the Veterans Administration, under the GI Bill, will give a resident benefits only if the hospital is approved for a specific number of years. Dr. Werrell reported that on the punch cards of applicants data were being requested on the period of residency training in hospitals and I assume on its adequacy. These data will furnish a rather stable base for setting a specific approval period. In a certain way, the results of the examinations of candidates will reflect over the years the adequacy or inadequacy of training in specific institutions. However, the candidate needs assurance that the program he is undertaking is adequate within the limits as defined by this Committee and the hospital.

"At this meeting a specific list of approved hospitals was verified. A specific list of hospitals which did not merit approval was verified. Dr. Thomas M. Durant was elected to take my place on the Committee on Educational Standards and the reëvaluation of the standards already in operation.

"The Committee voted to begin immediately by questionnaire a poll to ascertain the exact length and type of instruction given by approved hospitals. The next meeting of the Committee will be held in New York in June, 1953, in conjunction with the annual meeting of the American Medical Association."

Dr. Sturgis: "In connection with the Joint Commission on Accreditation of Hospitals, is our College carrying its load with regard to inspectors?"

Dr. Sloan: "We are carrying our load on the Joint Commission as it is set up at the present time, and the Commission is very happy to have us with them, both financially, socially and morally; but they also feel that we ought to be a sort of supreme court and final supervisor of certain of this work in approval of hospitals for residency training. We ought to have a more direct connection, and, therefore, they have suggested that in some fashion we consider the actual appointment of a man who would correlate the program of inspection and, perhaps, actually inspect for internal medicine only."

Dr. Palmer: "I think this rather important, because the American Medical Association really does not accept the responsibility for approving these residencies. They expect some group of internists to say that these residencies are approved as training in internal medicine. In turn, they would like to turn to the American Board of Internal Medicine and hold it responsible. The Board of Internal Medicine says, 'No. We are an examining group and we haven't the money, the time or the facilities to inspect hospitals for residency training. That ought to be the function of the American Medical Association or the American College of Physicians or someone else.' The American Medical Association says, 'We can't do it for internists. We are not internists.' So it rather looks to me that it is the American College of

Physicians which is left holding the bag, for it is the group that should accept responsibility. In other areas the responsibility has been accepted, as for instance, by the American College of Surgeons for surgery."

DR. STURGIS: "Is it your opinion we should do it and what would be the estimated financial outlay?"

DR. PALMER: "Yes, if it is to be done. I haven't estimated the cost."

DR. SLOAN: "The cost would be $15,000.00 for one man, covering salary and the major part of traveling expenses."

DR. BURGESS: "Perhaps a little clarification is needed. There are at present seventeen inspectors in the field. They are furnished by these three organizations that Dr. Sloan mentioned, but they are all doing the same thing. They have all had their work standardized. They were put through a course last year in Chicago to standardize the work; none of them inspects specifically for residencies. Those furnished by the College of Surgeons do just the same thing as those furnished by the Hospital Association and the American Medical Association.

"The question we have to decide is whether we are simply going to furnish another single inspector of the same type and have eighteen, where there are now seventeen. I do not recall it being suggested that we furnish anybody related to residencies in internal medicine. That is a different matter. None of these inspectors deal with residencies, except for the fact that those who are furnished by the American Medical Association's Council on Medical Education and Hospitals, of which there are eight, may concomitantly report on residencies as a separate matter, but not to the Commission; they report to the Council.

"I think the question is, are we going to do our part by furnishing one more general inspector?"

DR. SLOAN: "These inspectors are indoctrinated in such fashion that they are aiming to improve the hospitals. There is an ancillary service and general service in the approval of a hospital, but that approval is the first step in the training of internists. All those data are gotten together and submitted to the Joint Commission; the Advisory Committee has already passed on that. At the present moment there is no one whose specific duty is to inquire into the adequacy of the institution for internal medicine.

"Isn't it sensible that we support our share? I am not anxious to have this done today, because I think we can work this out with the Commission next Sunday morning. It seems to me sensible that we consider putting a man into the field and then we can enlarge his duties in some fashion, that he may be the correlating and coördinating inspector in the field of internal medicine. I think the Joint Commission will eventually put its stamp of approval not only on hospitals, but probably on the residency training situation. We will report back to the Regents later on what the Joint Commission feels about the suggestion that we get an inspector who will eventually become a coördinator of the program of internal medicine."

DR. BURGESS: "I think Dr. Sloan is quite right, and what he and I are interested in is whether the Board of Regents thinks well of supporting this program of the College doing its share. We all agree that the College, if anybody, should do it."

PRESIDENT MILLER: "Dr. Kern, do you have anything to report for the Membership Committee?"

DR. RICHARD A. KERN: "Mr. President, your Committee has nothing further to report in addition to what was said at the Joint Meeting of the Regents and Governors, when you, as President, referred to the survey of membership representation on faculties of medical schools. A reminder went out to those departments about correcting certain gaps that existed, and the fact is that there have come in a gratifying number of new proposals for membership as a result of that stimulus.

"It is pointed out, however, that it would be desirable to study in detail this response, checking on what new proposals come in and from what sources; and, in

addition, it might be desirable that a sustained and planned effort along these lines continue in the future. These might be made the duties of a future Committee on Membership."

PRESIDENT MILLER: "That completes the reports of Committees. We do need some intermediary thought about the 1955 meeting place and the appointment of a General Chairman."

SECRETARY LOVELAND: "It has been pointed out by several that we should appoint the General Chairman at the same time we select the meeting site. That would give him an opportunity to serve one year as a sort of General Chairman-Elect, providing the benefits of consulting with the current Committee and Officers on the Annual Session.

"The invitations for 1955 are largely restricted to two cities, Minneapolis and Philadelphia. There was one from San Francisco, but Dr. Dwight L. Wilbur, and some others, feel they could not accommodate the College in San Francisco well in 1955, because of certain other meetings. They would like to delay their invitation to 1956.

"There was another invitation for 1955 from Miami Beach, but information at hand does not indicate that they have the requisite facilities at this moment. Therefore, in my opinion, between now and Friday, when the meeting city will be selected for 1955, you should be thinking about Minneapolis and Philadelphia and about the General Chairman."

PRESIDENT MILLER: "It would have been helpful if the General Chairman for 1954 had been appointed a year ago, instead of at this meeting, so that he could have gone through all the preliminaries with our General Chairman this year. In fact, it was Dr. Hilton S. Read, our current General Chairman, who originally pointed out the advantages of having this officer appointed two years in advance."

. . . The meeting ADJOURNED at 3:40 P. M. . . .

Attest: E. R. LOVELAND,
Secretary

MINUTES OF THE BOARD OF REGENTS

ATLANTIC CITY, N. J.

APRIL 17, 1953

The second, separate meeting of the Board of Regents, during the 34th Annual Session, was held at Convention Hall, Atlantic City, N. J., Friday, April 17, 1953, convening at 12:45 o'clock, and presided over by Dr. LeRoy H. Sloan, newly inducted President of the College, and with Mr. E. R. Loveland acting as Secretary. The following were in attendance:

LeRoy H. Sloan	*President*
Cyrus C. Sturgis	*President-Elect*
George F. Strong	*First Vice President*
Alex. M. Burgess, Sr.	*Second Vice President*
William C. Chaney	*Third Vice President*
Richard A. Kern	*Secretary-General*
William D. Stroud	*Treasurer*
Asa L. Lincoln	
Walter L. Palmer	
Edward L. Bortz	
Herbert K. Detweiler	
Howard P. Lewis	
T. Grier Miller	
Charles A. Doan	*Chairman, Board of Governors*

President LeRoy H. Sloan announced that Mr. Ralph A. Claypoole, of the Educators Mutual Insurance Company, carriers of the College Group Insurance Plan, was present to answer any questions. He declared a quorum present and then introduced Mr. C. DeWitt Coffman, Executive Director, the Convention and Visitors Bureau of the Chamber of Commerce of Greater Philadelphia, who presented a formal invitation from the City of Philadelphia to the College to meet there in 1955. He covered in some detail the accommodations in the way of hotels, meeting rooms at Convention Hall, and other salient data. Dr. T. Grier Miller, Dr. William D. Stroud, Dr. Richard A. Kern and Dr. Edward L. Bortz, all of Philadelphia, cordially joined in the invitation.

PRESIDENT LEROY H. SLOAN: "We have an invitation from San Francisco for 1956 and we have an incomplete invitation from Miami for 1955, or some subsequent year. Miami might well be considered for some time in the future. Minneapolis has been presented by Dr. H. B. Sweetser at a previous meeting. In the regular course of this meeting, we shall vote on where we will hold the 1955 Annual Session. We thank Mr. Coffman for his invitation (whereupon Mr. Coffman retired).

"We shall proceed with the review of the Minutes of the preceding meeting of this body."

. . . Secretary Loveland read abstracted Minutes of the Board of Regents held on April 14, 1953, which were approved as read. . . .

PRESIDENT SLOAN: "Next is a communication from the American Board of Internal Medicine, in connection with the expiration of terms of present College representatives—Dr. Albert M. Snell (eligible for reëlection), Dr. Chester M. Jones (eligible for reëlection) and Dr. William B. Porter (not eligible for reëlection)."

DR. WALTER L. PALMER: "Mr. Chairman, I made that report at the preceding meeting and no further action is indicated at this time, because the Board must now act on the slate of nominees that was approved by the Regents. There are three men whose terms expire and the Board of Regents approved a slate of five men from whom we may select for any vacancy. If Doctors Snell and Jones are reëlected, then we shall select from the slate one member to succeed Dr. William B. Porter."

DR. SLOAN: "In regard to unfinished business, we have on the Agenda for discussion, if any, the matter concerning an A.C.P. inspector for the Joint Commission on Accreditation of Hospitals. I wonder if someone would make a motion that this be referred to the College Commissioners?"

. . . On motion by Dr. Edward L. Bortz, seconded by Dr. T. Grier Miller, put and carried, it was

RESOLVED, that the subject of an inspector for the Joint Commission on Accreditation of Hospitals be referred to the College Commissioners to explore the situation further. . . .

PRESIDENT SLOAN: "We have certain communications from the Board of Governors through Dr. Charles A. Doan, Chairman."

DR. CHARLES A. DOAN: "The Board of Governors met on April 15, 1953, and voted to present the following matters to the Board of Regents:

"(1) The questionnaire proposed by the Committee on Educational Policy was distributed to the Governors for critical suggestions for next year's Annual Session, and will be returned to the Secretary's Office.

"(2) The definitive reports of Dr. Carter Smith's Committee, having to do with recognition of retired and retiring Officers, Regents and Governors, recommend the following:

(a) To make available advance hotel reservations through the Secretary's Office.

(b) To make the special registration desk at the Annual Session available to this group.

(c) To prepare a parchment insert, or sticker, outlining the office or offices (and dates) held, for attaching to the American College of Physicians' Certificate of membership.
(d) To invite them to participate in the Convocation Procession, and to be seated either on the stage or in a special section in the front of the hall.
(e) To invite them to attend the Regents and Governors meetings, but without voting power.
(f) To invite them to attend the reception of the Regents, Governors and new members.

"The last three of these recommendations are to be optional, and to be included at the discretion of the President each year, depending upon the facilities, time and place of the meeting. These recommendations were adopted unanimously to be transmitted to the Board of Regents.

"(3) Dr. Lemuel C. McGee was elected to succeed himself as one of the three Governors on the Committee on Credentials, term to extend to 1956.

"(4) The suggestion was made to reconsider the sequence of the meetings of the Boards at the Annual Session; particularly, with the Regents' meeting to be held on Wednesday, after, rather than before, the Governors' meeting, which would then be held on Tuesday. This should facilitate the action of the Regents on matters transmitted for consideration by the Board of Governors prior to the Annual Business Meeting on Thursday.

"(5) It was unanimously voted to appoint a Committee to take under advisement and to make recommendations to the Board of Regents and to the President changes regarding the Annual Convocation. This Committee was immediately appointed, namely:

Dr. Irving S. Wright, *Chairman*
Dr. Chester S. Keefer
Dr. Lemuel C. McGee
Dr. Howard Wakefield

Their report is respectfully submitted at this time:

(a) That the Presidential Address be given on Tuesday afternoon, rather than at the Convocation.
(b) That the announcement of the Brower Scholars, Research Fellows and Latin-American Fellows be made at the Annual Business Meeting, Thursday afternoon, instead of being made at the Convocation. (These men may still be in the Procession and sit on the stage at the Convocation, if that is desired.)
(c) That the Convocational Speaker preferably be (1) a non-physician and non-scientist, and (2) a nationally known figure of outstanding ability as a speaker.
(d) That the citation for the medalists be significantly shorter.
(e) That the Pre-Convocation Assembly begin at 8:30 in the evening, the Convocation at 9:00, and the proceedings be concluded not later than 10:15.

"The Governors accepted these recommendations unanimously by acclamation.

"(6) By unanimous vote, the Governors recommend to the Regents that next year's Program Committee and the Executive Officers continue this year's innovation regarding the Governors and Regents Reception and Dinner to new members.

"(7) The Governors strongly urge that the Daily Bulletin, omitted this year, be reinstated at the next Annual Session for the convenience of locating members and friends in their respective hotel locations."

PRESIDENT SLOAN: "Thank you, Dr. Doan. Are there any comments?"

DR. ALEX. M. BURGESS: "Mr. Chairman, it would be well, in discussing this, to take certain portions; for instance, the matter concerning changing the dates of the meetings of the Regents and Governors. That should be acted upon separately. The reason for this recommendation is obvious to every one; it makes it possible for the Regents to act on recommendations of the Governors promptly instead of having a long waiting period. I would like to move that it is the sentiment of the Board of Regents that this change be made."

DR. PALMER: "In seconding that motion, may I raise this possibility for consideration, namely, that the Governors might meet on Monday, rather than on Tuesday. The College gets all Regents and Governors in for the meeting on Sunday, then there is nothing to do Monday morning or Monday noon, and then we seem to hurry things on Tuesday and Wednesday. I would like to amend Dr. Burgess' motion to read either Monday or Tuesday. Maybe next year the Program Committee might be thinking of starting the program Monday morning, which would delay the Governors' meeting until noon. It is my opinion that many members would like to arrive in Chicago in time for a Monday morning session, whether it be clinics, television, or something else. Another question is whether it is wise to continue this practice of having registration only on Monday morning."

SECRETARY LOVELAND: "There are two things that occur to me, which may not seem important to you. We have partially remedied the first matter, namely, registration, by initiating advance registration, but heretofore it has taken a long time to register the very large group reporting on Monday morning. If in Chicago we had an exceptionally large registration and we were holding them up from getting to a program, it would lead to much dissatisfaction. The second thing is that we have utilized Monday morning to get into operation, test and install all the public address systems, room setups, completion of installation of exhibits. Much of this is started the week before, yet it all has to be culminated and tested Monday forenoon."

PRESIDENT SLOAN: "Mr. Loveland, isn't the sense of this whole matter that we want some changes, shifting the Governors' meeting ahead of the second Regents' meeting? The time and programs really ought to be left up to the General Chairman and the Committee on Annual Sessions next year in Chicago. I do not think that we can consider them at this meeting, but I do feel that we get the sense of the intent of the Governors."

DR. BURGESS: "I accept Dr. Palmer's amendment to the motion, namely, that the Board of Governors meeting be held either Monday or Tuesday. There is nothing in the motion that indicates when on either day."

. . . The motion was put and carried. . . .

DR. PALMER: "Now, Mr. Chairman, may I move that we consider and act on Dr. Doan's report section by section?"

PRESIDENT SLOAN: "All right, Sir; on the matter of the recommendation of retiring Officers, Governors and Regents (re-reads that portion of the report)."

DR. PALMER: "With respect to that Certificate insert or sticker, I wonder if we are ready to act on that, or should further consideration be given? I do not know that I quite like that idea, but I think it needs to be further considered by some one. Would that be you, Mr. Loveland?"

SECRETARY LOVELAND: "I don't think the word 'sticker' ought to be used as such. If the Governors recommend a little insert on parchment, that might be all right, but you couldn't put a sticker on a parchment diploma. I am sure the Committee had

in mind a small insert that could be placed within the Certificate frame, down at the bottom of the Certificate, without defacing the Certificate, or covering any of the engraved copy. If any one didn't want to use this insert, they wouldn't need to."

PRESIDENT SLOAN: "Suppose we get along with some of the other items; first, making available advance hotel reservations to this group."

. . . It was moved by Dr. Cyrus C. Sturgis, seconded by Dr. Howard P. Lewis, put and carried, that this be approved. . . .

PRESIDENT SLOAN: "Second, maintenance of a special registration desk at the Annual Sessions for them."

. . . On motion by Dr. Howard P. Lewis, seconded by Dr. Cyrus C. Sturgis, put and carried, this recommendation was approved. . . .

PRESIDENT SLOAN: "Third, to prepare a suitable addition to the Certificate, outlining offices and dates, to be used in connection with the Certificate. I would suggest this be referred to Mr. Loveland's office for further consideration and handling."

. . . On motion by Dr. Cyrus C. Sturgis, seconded by Dr. T. Grier Miller, put and carried, this suggestion by President LeRoy H. Sloan was approved. . . .

PRESIDENT SLOAN: "Next, participation in the Convocation Procession, with seating either on the stage or a special section."

. . . On motion by Dr. T. Grier Miller, seconded by Dr. Howard P. Lewis, put and carried, this was approved. . . .

PRESIDENT SLOAN: "Next, that these gentlemen be invited to attend the Regents and Governors meetings, but without voting power."

. . . It was moved by Dr. Walter L. Palmer and seconded by Dr. Alex. M. Burgess that this be approved, and the matter was opened for discussion. . . .

DR. CYRUS C. STURGIS: "Would they participate in the discussion?"

PRESIDENT SLOAN: "I don't know."

DR. GEORGE F. STRONG: "It is a little ambiguous. You would have all the past Governors, Regents and Officers sitting in at all the meetings."

DR. DOAN: "I don't think very many would take advantage of the privilege. On the other hand, there are times when past Governors have very definite ideas about things and would like to express themselves. I don't see any reason why they shouldn't, as long as they do not have voting power, in terms of the organization."

PRESIDENT SLOAN: "Could we limit their discussion?"

DR. DOAN: "That, I think, should be up to the presiding officer. I think that could be regulated by the Chair."

PRESIDENT SLOAN: "Is it the sense of this recommendation to allow former Governors to attend Governors' meetings only?"

DR. DOAN: "I would eliminate the Sunday afternoon meeting, which is a joint session, have the annual Governors business meeting for the Governors and the annual Regents meeting for the Regents; these might be the ones to which they would be invited."

PRESIDENT SLOAN: "Would you accept that, if we rewrite it a bit?"

DR. BURGESS: "Does it say by former members of the respective bodies? That is what is intended."

PRESIDENT SLOAN: "That is the intent. Is that all right?"

DR. DOAN: "Yes, sir."

. . . The motion was put and carried. . . .

PRESIDENT SLOAN: "Next, that they be invited to attend the Reception for Regents, Governors and new members."

DR. PALMER: "I wonder, Mr. President, if some leeway shouldn't be left there, because the policy might be changed from time to time?"

PRESIDENT SLOAN: "The last three recommendations are to be optional, and are

to be included at the discretion of the President each year. I would add President and Executive Committee."

DR. DOAN: "The thought was that that should be left each year to the Executive Officers and the President regarding facilities and funds available."

DR. PALMER: "That is satisfactory with me, but did you mean the Reception only, or the Reception and Dinner?"

DR. DOAN: "If they are together, it would have to be both."

PRESIDENT SLOAN: "Past Presidents have always been invited to the Sunday night Dinner."

DR. PALMER: "This would include authorizing the President and the Executive Officers inviting then all past Presidents, past Regents and past Governors to the Cocktail Party and to the Dinner?"

DR. DOAN: "It isn't automatic; it would each year have to be decided upon."

DR. PALMER: "I think it should specifically include the Cocktail Party and Dinner, rather than the Cocktail Party alone."

PRESIDENT SLOAN: "Will you permit me to refer this to the President and the Executive Committee? It is a big expense."

. . . On motion by Dr. Cyrus C. Sturgis, seconded, put and carried, this particular item was referred to the President and the Executive Committee. . . .

PRESIDENT SLOAN: "Next is the suggestion to reconsider the sequence of meetings. That has been passed already. Next are the changes suggested with regard to the Annual Convocation. The suggestions are referred to the Officers and the Board of Regents; first, that the Presidential Address be given on Tuesday afternoon, rather than at the Convocation."

DR. STURGIS: "What is the purpose of that, Dr. Doan?"

DR. DOAN: "To shorten the Convocation."

DR. STURGIS: "Do you really think it is too long?"

DR. DOAN: "Dr. McGee, the Marshal, was the first one in the discussion to get up and recommend that this be an accomplished fact. He was a member of the Committee, and with his two years of experience, he is one of the men who are recommending this streamlining of the Convocation. It was thought there should be more time for dinner, for example, that evening and for parties of that sort, if one didn't have to begin to get ready for the Procession at 7:45. It was suggested that shortening the proceedings, the Convocation could start later, thus giving more time for dinner and preparation. They felt there should be one address, and that should be by an outstanding individual, such as Foster Dulles, or someone of that caliber, who would be an attraction to the Convocation. There should be a plan by which the Convocation would be as high a point in our evening programs as was the symphony concert on Sunday night, and that we try to have three attractions that would draw a large proportion of our members, and that the Convocation in honor of these men who are being inducted would serve what was suggested by the panel today in our public relations outside of the field of scientific medicine—that it should be something that would be pertinent to the time of the Convocation and be something that would not be medical necessarily, that it have something to do with the social, economic or political—not partisan politics—activities in which physicians should be interested. The speaker should have something real to give, and we feel that with a body as large as this we could well hope to attract a person of national eminence and prominence to speak with the College as a sounding board. Also, it would give the President's address a larger audience at the beginning of the afternoon scientific session on Tuesday."

DR. STRONG: "You would have a larger audience at the Convocation, if you got a national figure, and the President could still give his talk the same night."

DR. BURGESS: "That would eliminate the factor of cutting down time."

DR. DOAN: "We thought the speaker should be limited to thirty minutes, and the Convocation should last no more than an hour. 'No souls are saved after the first fifteen or twenty minutes,' was the thought of the Governors."

PRESIDENT SLOAN: "Who do we give the Convocation for? What is its purpose?"

DR. STURGIS: "The purpose of the Convocation is really for the new members and the awarding of these honors."

DR. PALMER: "As far as I can make out, the new members don't get too thrilled by the Convocation. Dr. Doan has brought out that the attendance is always small. It is limited to the Officers, Governors and Regents, their wives and the new members and their wives and families, who come to see them inducted. I think it is a pretty unpopular night for the membership at large."

DR. STURGIS: "There is a good deal of merit in these recommendations, and I think we ought to give them careful consideration, because I think the Convocation can be improved over what it is. I would like to move that a special committee of the Regents be formed to consider this recommendation and report at our meeting in the autumn. This refers to all matters concerning the Convocation."

. . . The motion was seconded by Dr. Edward L. Bortz, put and carried. In clarifying the motion, it was agreed that it be a committee of five Regents, appointed by the President, to report back at the next meeting of the Board of Regents in November, 1953. . . .

DR. HOWARD P. LEWIS: "I doubt if the members would like to interrupt the scientific program by a President's address."

PRESIDENT SLOAN: "Would you mind if next year the President's address is cut down a little bit?"

DR. LEWIS: "I think it should come properly either at the Annual Business Meeting or at the Convocation."

DR. DOAN: "Mr. President, a precedent has been set in meetings of some other societies, in the Association of American Physicians' meeting, and the young Turks' meetings, and some others, that the President's address be given as part of the scientific meetings. It is much enjoyed and very appropriate, and I am strongly for that."

PRESIDENT SLOAN: "I think we get the sense of this discussion.

"The Committee on Postgraduate Courses wishes approval of a course to be given at Ohio State University College of Medicine in Radioisotopes, under the supervision of Dr. Charles A. Doan."

. . . On motion by Dr. Cyrus C. Sturgis, seconded by Dr. T. Grier Miller, put and carried, such approval was given. . . .

. . . In accordance with regulations of the By-Laws, Dr. Richard A. Kern was re-elected Secretary-General and Dr. William D. Stroud was reëlected Treasurer. . . .

PRESIDENT SLOAN: "We shall now proceed with the election or appointment of Committees."

. . . In accordance with provisions of the By-Laws, or regulations of the Board of Regents, the following Committees were elected or appointed for 1953–54: (Personnel of these committees was published in the June, 1953, issue of this journal, and therefore is not repeated here.)

PRESIDENT SLOAN: "We now come to the official election of the General Chairman for the Chicago Annual Session."

. . . Dr. Walter L. Palmer moved and Dr. Alex. M. Burgess seconded the nomination of Dr. Howard Wakefield as General Chairman of the 35th Annual Session, Chicago, Ill., April 5–9, 1954; the motion was put and carried. . . .

PRESIDENT SLOAN: "Next is the selection of the 1955 Annual Session city."

DR. STURGIS: "Mr. President, I would like to move that the 1955 Annual Session be held in Philadelphia during the week of April 25–29, which is held in reserve for

us. Easter falls on April 10 that year and this date is sufficiently delayed not to interfere with Easter week, and it is the week immediately preceding the Atlantic City meetings of the Association of American Physicians, and other bodies."

. . . The motion was seconded by Dr. Alex. M. Burgess, put and carried. . . .

PRESIDENT SLOAN: "The next matter of business is the selection of the General Chairman of the 1955 Annual Session."

. . . Dr. Richard A. Kern moved and Dr. Cyrus C. Sturgis seconded the nomination of Dr. Thomas M. Durant; the motion was put and carried. . . .

DR. KERN: "I think the election of the General Chairman an extra year in advance is an ideal arrangement, because it means he can have all of his committee group set up and they can be assigned to work and observe in Chicago, and profit by the experience."

. . . President LeRoy H. Sloan introduced a brief discussion concerning some special and adequate recognition of men who have worked year in and year out for the College, and asked members of the Board to be thinking about the appropriate procedure, between this and the next meeting of the Board. . . .

Adjournment—1:50 P.M.

Attest: E. R. LOVELAND
Secretary

OBITUARIES

DR. IRVING R. BELL

Dr. Irving Russell Bell, F.A.C.P., died in Edmonton on May 9, 1953, of myocardial infarction.

Dr. Bell was born in Caledon, Ont., in 1883. He graduated from the University of Toronto with the degrees of A.B. in 1906 and M.D. in 1909. Following a period of interne training at the Erie County Hospital in Buffalo, N. Y., Dr. Bell began practice in Edmonton, where he continued to be active until the time of his death. He was recognized as a well trained, sound internist and consultant, with critical keenness of judgment and a kindly interest in his colleagues, students and patients.

Dr. Bell gave generously and effectively of his time and enthusiasm to medical education. He was Professor of Therapeutics and Assistant Professor of Clinical Medicine in the University of Alberta Faculty of Medicine. A loyal and active member of the attending staff of the Royal Alexandra Hospital, Dr. Bell held the position of Chief of the Department of Medicine for many years. He gave leadership to organized medicine in Alberta, acting as Secretary in 1924 and as President in 1926 of the Alberta Medical Association. Dr. Bell was elected President of the Edmonton Academy of Medicine in 1936. In addition to his Fellowship in the American College of Physicians, which he obtained in 1943, he was a Fellow of the Royal College of Physicians of Canada. Three of his sons are members of the teaching staff in the Faculty of Medicine of the University of Alberta.

The name of Irving Russell Bell will endure in the memory of his colleagues, his students, his patients and his friends as an outstanding internist, an inspiring teacher, a lovable physician and a worthy gentleman.

JOHN W. SCOTT, M.D., F.A.C.P.,
Governor for Alberta

DR. RICHARD B. DURNIN

In the death of Dr. Richard Brown Durnin, F.A.C.P., in Great Falls, Montana, on December 30, 1952, the Montana-Wyoming district of the American College of Physicians and the State of Montana lost one of their finest physicians. The cause of his death was noted as coronary heart disease, myocardial infarction, and acute ventricular failure. His was a restless soul, and he continued some practice almost until the day of his death.

Dr. Durnin was born May 10, 1882, in Dungannon in the Province of Ontario. He received his degree of Bachelor of Medicine from the University of Toronto Faculty of Medicine in 1908 and did postgraduate work at Bellevue Hospital in New York City from 1908 to 1910. He practiced briefly in Minot, N. D., and came to Great Falls to begin the practice of internal medicine on May 1, 1910, where he practiced continuously, except for his Army service in the First World War, until his death in 1952.

In 1917, with three other men, Dr. Durnin founded the Great Falls Clinic, which stands today as a splendid monument to his foresight, personal and scientific honesty, and to his ability to draw good men to him and to hold them.

He became a Fellow of the American College of Physicians in 1923 and was certified by the American Board of Internal Medicine in 1937.

The wideness of his interests was reflected in his extensive ranching interests, his directorship in the Montana Power Company and his Masonic affiliations, which included membership in the Blue Lodge, York Rite (Great Falls Consistory) and

Algeria Shrine Temple. He was past President of the Cascade County Medical Society and a member of the Montana and American Medical Associations.

His finest eulogy has been stated by one of his associates in the Department of Medicine in the Clinic which he helped to found. "As you know, he was always a bit gruff, but always forthright and honest; and we knew precisely where we stood with him. Most important of all, while he often disagreed with some of our methods of practice, he would simply express his disagreement honestly but never hinder us in our execution. This, I always felt, was a great thing for the good of the younger men in his department, myself included. Furthermore, he might make our faces red and our ears sting but always backed us up to the hilt with patients. Without some one like him as my senior when I came out here, I would have been hampered in following my hunches. I have tried to follow his forbearance in my association with younger men who have come here since."

This statement expresses much better than many fine phrases how all of us who knew Dr. Durnin through the years felt about him. Withal, we knew him as a man of much warmth and kindliness, and as a splendid colleague and consultant. His place in Montana Medicine and in the American College of Physicians will not be easily filled.

HAROLD W. GREGG, M.D., F.A.C.P.,
Governor for Montana and Wyoming

DR. PAUL L. PARRISH

Dr. Paul Larnard Parrish, a Fellow of the American College of Physicians since 1920, died on January 29, 1953, of cirrhosis of the liver.

Dr. Parrish was born in Johnstown, N. Y., on April 15, 1876. He graduated from Bellevue Hospital Medical College, receiving the medical degree in 1898. He held the following appointments: Visiting Physician of the Seaside Hospital for Babies, Assistant and Attending Physician at St. Christopher's Hospital for Babies for ten years, former Assistant Attending Physician, Children's Department, Kings County Hospital, where he later was Director of Pediatrics. He became Director Emeritus of Pediatrics of St. John's Episcopal Hospital in 1945; he had been Consulting Pediatrician to the Wyckoff Heights Hospital since 1925, the Brooklyn Eye and Ear Hospital since 1935, and to the Methodist Hospital since 1932. He had been Professor Emeritus of Clinical Pediatrics at the State University of New York College of Medicine at New York City since 1934.

Dr. Parrish was a member of the local draft board during World War I, a Diplomate of the American Board of Pediatrics, former President of the Brooklyn Pediatric Society, former Chairman of the Kings County Pediatric Society, and President in 1942 of the Brooklyn Academy of Pediatrics. He was also a member of the Medical Society of the County of Kings, American Medical Association, Associated Physicians of Long Island, Pan American Medical Association and the American Academy of Pediatrics.

The friends and colleagues of Dr. Parrish note his passing with profound sorrow and regret.

IRVING S. WRIGHT, M.D., F.A.C.P.,
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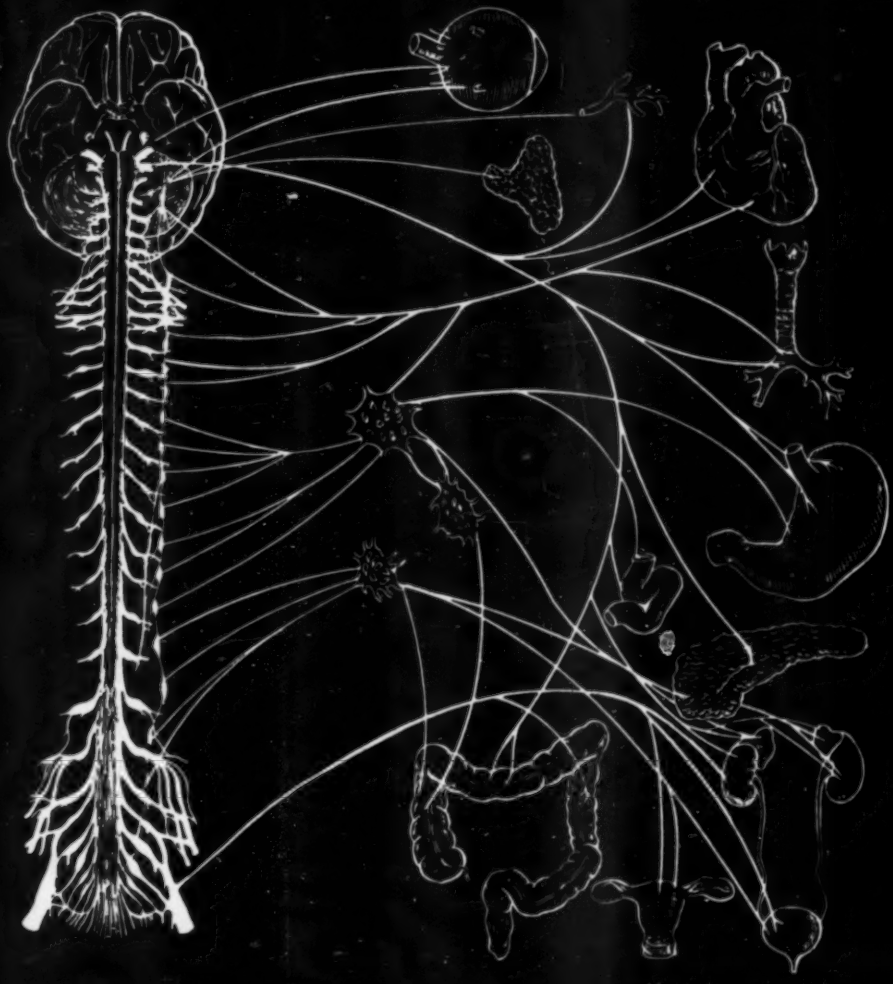

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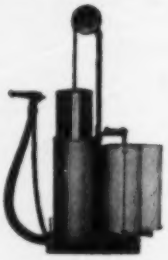

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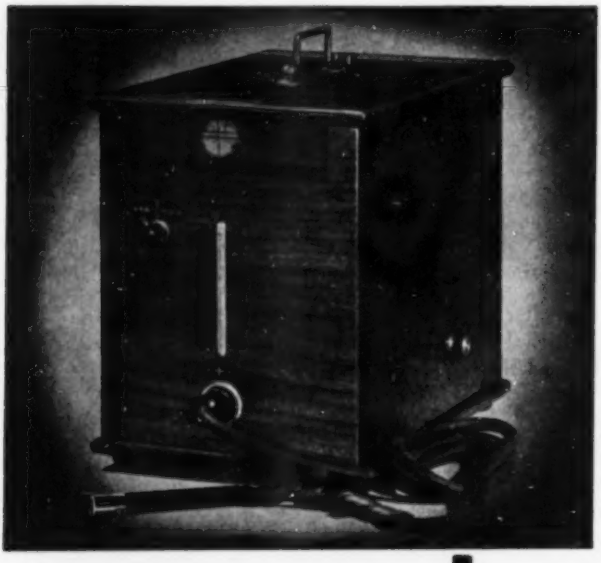

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